WHO/IVB/12.04
ORIGINAL: ENGLISH

Global vaccine safety blueprint

The landscape analysis

Immunization, Vaccines and Biologicals

World Health Organization

WHO/IVB/12.04
ORIGINAL: ENGLISH

Global vaccine safety blueprint

The landscape analysis

Immunization, Vaccines and Biologicals

World Health Organization

The Department of Immunization, Vaccines and Biologicals thanks the Bill and Melinda Gates Foundation whose financial support has made the production of this document possible.

This document was published by the
Quality, Safety and Standards unit
of the Department of Immunization, Vaccines and Biologicals

Ordering code: WHO/IVB/12.04
Printed: March 2012

This publication is available on the Internet at:
www.who.int/vaccines-documents/

Copies of this document as well as additional materials on immunization, vaccines and biologicals may be requested from:
World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* + 41 22 791 4227 • *Email:* vaccines@who.int •

Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

Acknowledgements

The development of the Blueprint landscape analysis was supported by a grant from the Bill and Melinda Gates Foundation.

Authors of the respective sections are listed below. They received guidance from Collaborative Group members and the WHO secretariat.

WHO would like to express its sincere thanks to all contributors for their support and judicious advice.

Activity 1.1 - The capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries

Principal Investigator:	Dr Jan Bonhoeffer
Co-investigators:	Dr Yulin Li, Dr Daniel Weibel
Collaborative Group Liaison:	Dr Juhani Eskola, Dr Heidi Larson **Brighton Collaboration**

Activity 1.2 - Enhanced strength-weakness-opportunity-threat analysis of international vaccine safety activities

Principal Investigator:	Dr Jan Bonhoeffer
Co-investigators:	Dr Yulin Li, Dr Daniel Weibel
Collaborative Group Liaison:	Dr Alex Dodoo, Dr Sunheang Shin **Brighton Collaboration**

Activity 1.3 - Survey of regulators

Principal Investigator:	Dr Janice Graham
Co-investigators:	Dr Alexander Borda-Rodriguez, Dr Farah Huzair
Collaborative Group Liaison:	Dr Murilo Freitas Dias **Technoscience and Regulation Research Unit, Faculty of Medicine, Dalhousie University**

Activity 1.4 - Survey of vaccine manufacturers

Principal Investigator:	Dr Elena Achkasova
Co-investigators:	Dr Trevor Gibbs, Dr Lars Schmiedeberg, Dr Jan-Willem van der Velden
Collaborative Group Liaison:	Dr Sunheang Shin, Dr Stanley Plotkin **International Institute for the Safety of Medicines Ltd.**

Activity 1.5 - Baseline assessment of the vaccine safety systems in the WHO global post-marketing surveillance network countries

Principal Investigator:	Dr Radmila Mirzayeva
Collaborative Group Liaison:	Dr Alexander Dodoo, Dr Heidi Larson, Dr Sunheang Shin **Independent Consultant**

Activity 1.6 - Analysis of NRA assessment data

Principal Investigator:	Mr Lahouari Belgharbi
Collaborative Group Liaison:	Dr Murilo Freitas Dias **World Health Organization (WHO)**

Activity 1.7 - Financial assessment

Principal Investigator:	Ms Anaïs Colombini
Co-investigators:	Mr Jean-Bernard Le Gargasson
Collaborative Group Liaison:	Dr Steve Black, Dr Heidi Larson **Agence de Médecine Préventive (AMP)**

Abbreviations & acronyms

ABC	Automatic Brighton Classification
AEFI	adverse events following immunization
AFR	WHO African Region
AMP	Agence de Médecine Préventive
AMR	WHO Region of the Americas
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention (USA)
CIOMS	Council for International Organization of Medical Science
COFEPRIS	Comisón Federal para la protección contra riesgos sanitario (Mexico)
CP	country profile
DCVRN	Developing Countries' Vaccines Regulators Network
DPT	diphtheria-tetanus-pertussis vaccine
EMA	European Medicines Agency
EMR	WHO Eastern Mediterranean Region
EPI	Expanded Programme on Immunization
EUR	WHO European Region
FDA	United States Food and Drug Administration
FTE	full time equivalent
GACVS	Global Advisory Committee on Vaccine Safety
GMP	good manufacturing practice
GVS	Global Vaccine Safety (project)
GVSD	Global Vaccine Safety Datalink
H	health-facility (level)
HDI	human development indicators
IEC	information, education and communication
ISO	International Standards Organization
IVB	Immunization, Vaccines and Biologicals (WHO)
IVSA	international vaccine safety activities
IVSI	international vaccine safety initiatives

LIC	low-income country
LMIC	low- and middle-income countries
LSHTM	London School of Hygiene and Tropical Medicine
MOH	Ministry of Health
N	national (level)
NA	not applicable
NCL	national control laboratory
NGO	non-governmental organization
NIP	National Immunization Programme
NPV	negative predictive value
NRA	national regulatory authority
NVSS	national vaccine safety system
PAHO	Pan American Health Organization
PMS Network	post-marketing surveillance network
PMS	post-marketing surveillance
PPV	positive predictive value
PSUR	periodic safety-update report
S	sub-national (level)
SAE	severe adverse event
SEAR	WHO South-East Asia Region
SOP	standard operating procedure
SWOT	strength-weakness-opportunity-threat
UMC	Uppsala Monitoring Centre
UN	United Nations
USA	United States of America
VS	vaccine safety
WHO	World Health Organization
WPR	WHO Western Pacific Region

Preface

Very few public-health interventions have been as successful as immunizations in preventing untimely deaths. Over the past thirty-five years, vaccines have provided substantial and highly cost-effective improvements to human health, particularly to that of children. As immunization systems mature, immunization safety has become pivotal in determining the success or failure of national vaccine-preventable disease control programmes.

Although hundreds of millions of doses of vaccine are used every year in developing countries, assessments of regulatory authorities, conducted by WHO, demonstrate that few of the developing countries' programmes have the ability to monitor and assure the safe use of vaccines. Now more than ever, it is clear that vaccine safety issues are not merely a developing or developed country phenomenon, but a global phenomenon. WHO has therefore proposed developing a blueprint for a global, regional and country level vaccine safety assessment and response system.

This initial step of the global vaccine safety blueprint project included a set of studies that analysed the existing vaccine safety infrastructure in low-income countries. These studies have provided the foundations for the development of a strategic plan that defines the indicators of a minimal capacity for ensuring vaccine safety, and proposes a concerted approach to enhance global vaccine safety activities, with a focus on national capacity in the world's poorest countries up to the minimal capacity. In addition, the blueprint includes an illustrative workplan with a budget and management principles.

This report summarizes the findings of seven detailed studies conducted during the first phase of the global vaccine safety blueprint project. The studies provided the empirical basis for developing the blueprint strategies and work planning, and are referenced throughout the blueprint documents. Three stakeholder surveys (vaccine safety experts, industry and regulators), three systems analyses (national regulatory functions for post-marketing surveillance of vaccine adverse events, vaccine pharmacovigilance infrastructure in a sample of low- and middle-income countries, and existing international vaccine safety initiatives) and one financial analysis are presented here.

The capacity and needs of post-marketing vaccine safety monitoring in Low- and Middle-Income Countries (LMIC)

Executive summary

WHO is developing a global vaccine safety blueprint to improve existing vaccine safety systems in low- and middle-income countries (LMIC). In preparation for the blueprint, information on the perception of vaccine safety experts about the performance of vaccine safety systems in LMIC, as well as their expectations and recommendations, was sought.

To outline local experience, available infrastructures, needs and priorities of vaccine safety monitoring expressed in LMIC, we performed a survey of vaccine safety stakeholders with different professional backgrounds in LMIC. Experts were randomly sampled by country economic status, WHO region and population size. Their relevant perspectives were elicited via questionnaire by four scientific areas of vaccine safety monitoring. Follow-up clarifications were implemented when appropriate.

Of the 182 professionals who initially agreed to participate, 78 (43%) coming from 28 LMIC, returned the survey. Of these, 89% coming from 26 LMIC, expressed the need to improve the capacity and quality of vaccine safety monitoring in their countries. The main needs expressed were support for training (80% from 27 LMIC) and harmonized methods, including standardized case definitions (74% from 26 LMIC). Eighty-two percent of professionals coming from 24 countries report to have spontaneous reporting systems. Of these, 52% coming from 20 countries, indicate actual detection of reports. Fifty-six percent, coming from 19 countries, indicated the existence of at least basic health databases. However, only 15%, coming from six countries, reported conducting epidemiological studies using these resources. Forty-five percent, coming from 14 countries, wish to achieve the ability to link health-care databases. Forty-five percent, coming from 18 countries, indicate that they are partially relying on vaccine safety information from other countries. Thirty percent, coming from 15 countries, requested improved international collaboration and, as high as 93%, coming from 26 LMIC, expressed the need for support from an international consortium.

Ensuring the safety of vaccines is considered important by public-health experts from LMIC. There is a need to improve the quality of existing vaccine safety data, to enhance local analytic capacity, to establish health-care databases and to enhance information sharing within and across countries. This could best be accomplished through a concerted effort to provide training and harmonized tools, and an international support structure, so that countries can perform vaccine safety functions effectively.

1. Background

Hundreds of million of doses of vaccine are used every year in developing countries. Many vaccine products are now either primarily licensed in, or developed for, exclusive use in low- and middle-income countries (LMIC). However, 65% of WHO Member States, including the majority of LMIC, do not have a functional post-marketing monitoring system to monitor and assure a safer use of vaccines. Safety issues have derailed local vaccine programmes. It is essential that these countries have the capacity to detect, investigate and respond to vaccine safety concerns.

The resources and expertise needed to establish such systems locally, and globally, are limited. It is essential to discern where to prioritize and how to federate global resources to improve functional vaccine safety monitoring, investigation and response systems, particularly in LMIC. To address these needs, WHO is developing a global blueprint to describe strategic plans, budget and funding options and governance principles of an integrated vaccine safety consortium. In preparation for the WHO blueprint, information is needed on local capacity and the needs of post-marketing vaccine safety monitoring in LMIC.

2. Objectives

These are, to outline local experience, strategies, needs and priorities of vaccine safety monitoring in LMIC.

3. Methods

3.1 Study design and population

A standardized survey was designed and implemented among vaccine safety experts with different professional backgrounds in LMIC, to draw out their perception, expectations or recommendations regarding vaccine safety monitoring systems in their particular countries.

To ensure the representativeness of the sample and reduce selection bias, we randomly selected one country from each cluster stratified by WHO geographic regions (AFR, AMR, SEAR, EUR, EMR, WPR), country economic status classified by the World Bank in 2010 (low income, lower middle income) and population size (≤10, ≤100, >100 million). Twenty-seven countries were identified based on random sampling (See Appendix I). At the time of the closing date for data collection, we had received completed surveys from 20 of the countries selected. In this report, we have therefore included data from an additional nine LMIC in which qualified participants were able to be contacted.

Within each country, we have tried to identify at least one representative from five different professional backgrounds: regulatory authority; public health; academia and patient care; health consumer representative, and manufacturer, where available. Participants were identified through a WHO contact list of national regulatory authorities (NRA) and lists were provided by the blueprint collaborative group or WHO regional offices, the Brighton Collaboration (BC) member list, recommendations from Brighton Collaboration members, PubMed and extensive internet search, or recommendations from local professionals. Recruitment of qualified LMIC stakeholders was done by email invitations, plus phone calls where necessary.

3.2 Questionnaire development

A structured survey was developed which established an international initiatives inventory, assessing local/national available infrastructures and previous experience, development plans and needs for each of the four areas of vaccine safety monitoring: (1) concern detection; (2) concern verification; (3) causality assessment; (4) risk communication (See Appendix II). The questions were either structured or open questions. The questionnaire was tested in three countries not participating in the main study (Brazil, Ghana and South Africa). The questionnaire was then revised according to comments from the consultative group review and preliminary analyses of the pilot testing. The final version of the questionnaire was then translated from English into six other languages, including Arabic, Chinese, French, Portuguese, Russian and Spanish.

3.3 Data analysis

Participants referring to pre-licensure concerns in their responses were excluded from primary analysis. Descriptive analyses were done with IBM SPSS software (version 19.0, SPSS Inc., Chicago, IL). Free texts were interpreted and classified into categories. Interesting and residual findings from open questions that could not be grouped into categories are instead described in the results and discussion. Results were stratified by co-variables, such as economic status, when appropriate.

4. Results

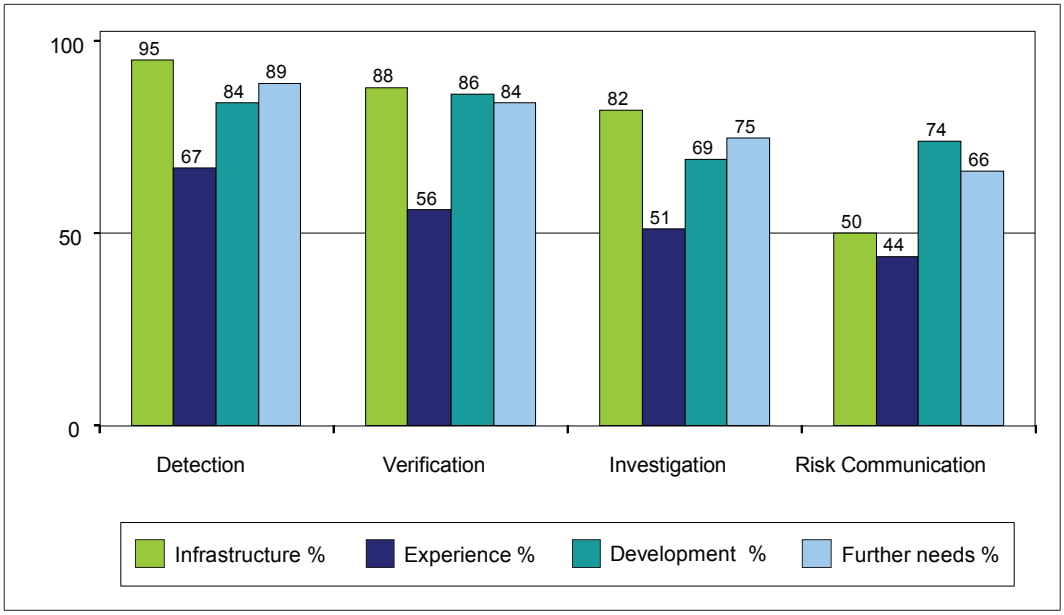
4.1 Description of study participants

Five hundred and fifty-eight professionals from 70 countries were screened as potential survey participants; 182 of them from 47 countries were sent a questionnaire, and 78 from 28 countries responded. Seventy-seven of the 78 returned surveys were included in the primary analyses. Thirty-eight percent of the professionals are from 11 low-income countries, while 62% are from 17 low to middle-income countries. Professional background distributions include regulatory authority (18%), public-health organizations (47%), academia or patient care (27%), manufacturers (6%) and health consumer representatives (3%). This distribution would seem to reflect the underlying distribution of organizations involved with vaccine safety in LMIC.

4.2 Consistent pattern of "available infrastructure – lacking experience – needs for improvement"

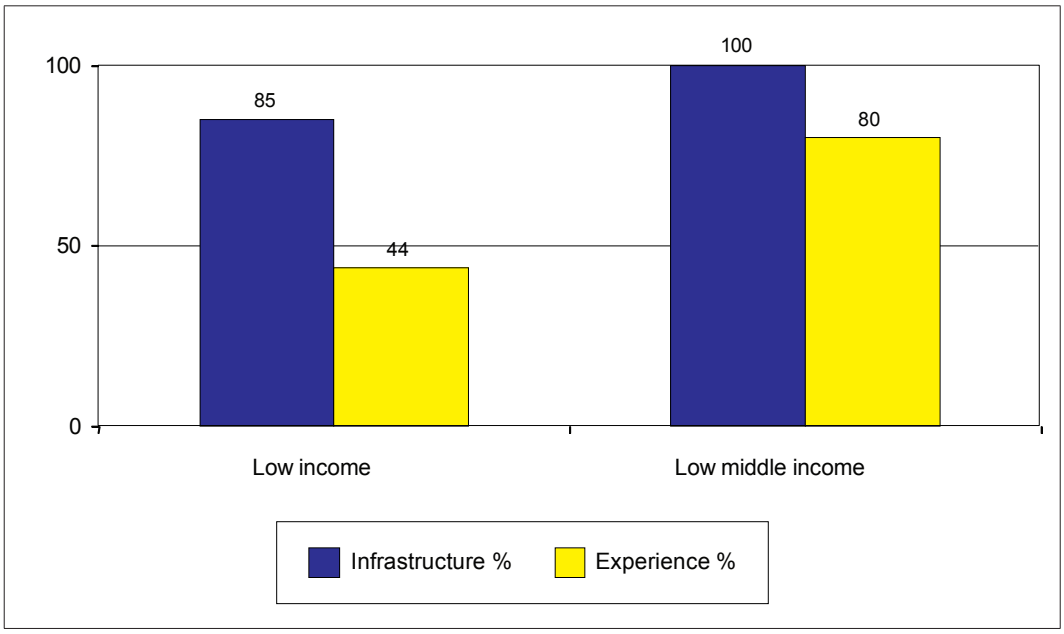
Across the areas of concern detection, verification and investigation, high proportions of professionals indicated at least one available element of infrastructure (95%, 88%, 82%, respectively), while much lower proportions of them indicated actual experience (67%, 56%, 51%, respectively). The consistent mismatch of perceived available infrastructure and experience may suggest suboptimal utilization of existing systems. This may be explained by the relatively recent attention to developing vaccine safety systems. Hence, infrastructure is starting to be put in place, but there is still limited experience. Furthermore, system development is ongoing and extensive needs are highlighted in all areas, thus indicating an intention to improve the current situation (Figure 1, Table 1). Overall, risk communication is the most underdeveloped area.

Figure 1: Perceived available infrastructure, previous experience, ongoing development and further needs, by area of activity



Stratification by country economic status shows that the mismatch between available infrastructure and experience for concern detection exists mainly in low-income countries (LIC) with 85% professionals coming from 10 LIC versus 44% coming from five LIC. In addition, countries with a higher income level were more likely to detect concerns than countries with a lower income level (80% professionals coming from 17 low- middle-income countries versus 44% from five LIC) (Figure 2).

Figure 2: Perceived infrastructure and experience in detection of vaccine safety concerns by country economic status



Although 56% of professionals, coming from 19 countries, indicated the existence of at least basic health-care databases, only 15%, coming from six countries, reported conducting epidemiological studies using these resources (Table 1).

Table 1: Comparisons of perceived infrastructure, experience and overall needs for selected items

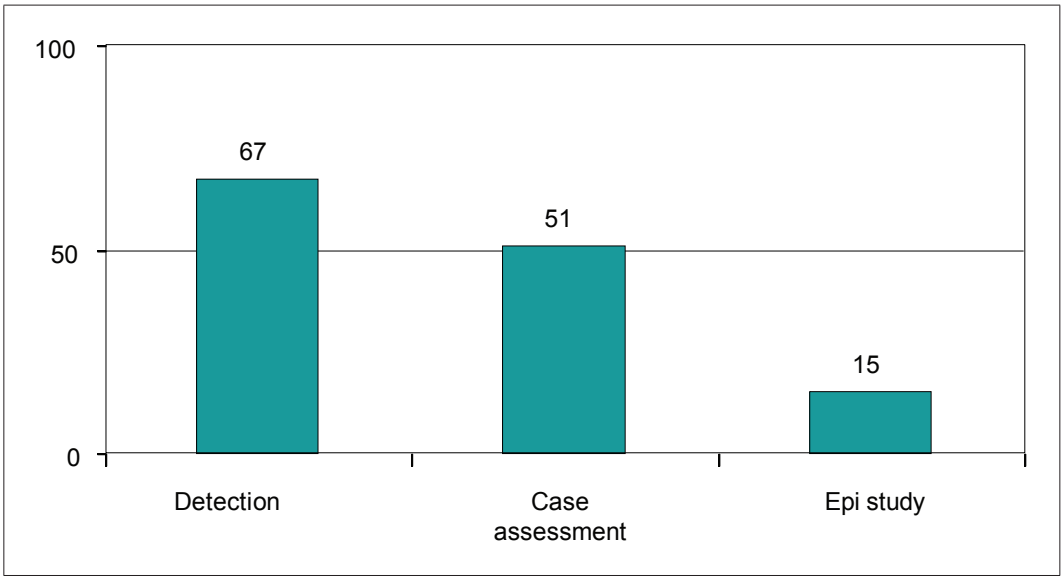
	Pertinent area	% professional (from no. of countries)		
		Infrastructure	Experience	Overall needs‡
Spontaneous reporting	Detection	82% (24)	52% (20)	78% (25)
Standardized case definition	Verification	70% (24)	33% (14)	74% (26)
Expert committee	Verification	66% (22)	33% (13)	64% (23)
Immunization records	Verification	60% (19)	29% (9)	63% (22)
Health-care database	Investigation	56% (19)	15% (6)*	49% (22)
Media tracking	Detection	53% (17)	14% (5)	52% (17)
Observed versus expected analyses	Verification	38% (13)	15% (6)	37% (14)

* Experience in using epidemiologic studies to investigate associations of vaccine safety concerns was compared with health-care databases available.

‡ Overall expressed needs was calculated for individuals: "yes" to the same item in either "existing programme" and "further needs" was counted as "yes" to the corresponding item in "overall expressed needs".

Sixty-seven percent of professionals, coming from 23 countries, stated experience in concern detection. Concern investigation was based on case review by 51% of experts, coming from 18 countries. Conduction of epidemiological studies has only been indicated by 15% of professionals, coming from six countries (Figure 3).

Figure 3: Experience with concern detection and investigation by method in LMIC (percentage of professionals)



4.3 Major expressed needs and capacity to be achieved

As shown in Table 2, the major needs expressed include: training; harmonized tools or methods, such as standardized case definitions; expert committee; capacity of data analysis and interpretation; vaccine registry; health-care databases; accessibility to medical source and immunization data, and improving perception and beliefs of vaccine safety.

When asked about the local minimal capacity to be achieved, the improved ability to link health-care databases was cited by 45%, coming from 14 countries. Improved ability to validate vaccine safety reports was also cited as desirable by 36% of professionals, coming from 14 countries (Table 2).

Risk communication is the least developed area. Fifty percent of the professionals indicated infrastructure availability and 44% of them stated previous experience (Figure 1). As many as 78% of professionals, from 25 countries, cited an overall need for training in this area (Table 2).

Table 2: Ongoing development and overall needs by the four scientific areas (selected items)

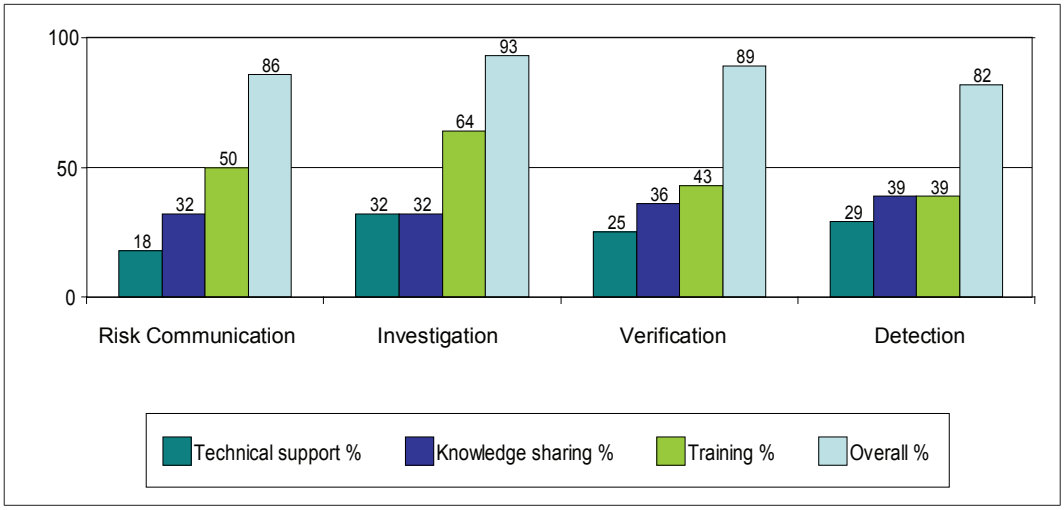
	% professional (from no. of countries)	
	Ongoing development	Overall needs‡
Concern detection		
Training	62% (20)	80% (23)
Spontaneous reporting	67% (24)	78% (25)
Stimulated reporting	51% (20)	59% (24)
Health database analyses	47% (18)	55% (19)
Media tracking	47% (17)	52% (18)
Perception and beliefs	27% (13)	45% (18)
Reports from other countries	38% (17)	40% (17)
Concern verification		
Training	62% (22)	80% (27)
Standardized case definitions	63% (24)	74% (26)
Experts committee	64% (23)	73% (24)
Immunization records	56% (21)	63% (22)
Access to medical source and immunization data	43% (17)	48% (19)
Observed versus expected analyses	32% (15)	37% (15)
Concern investigation (causality assessment)		
Training	53% (20)	78% (27)
Experts and knowledge	45% (18)	63% (23)
Capacity of data analysis and interpretation	41% (17)	56% (22)
Vaccine registry	41% (19)	53% (21)
Health-care databases	43% (21)	49% (22)
Regular quality control	36% (17)	47% (21)
Collaboration with other countries	21% (12)	30% (15)
Regional data sharing/accessibility	21% (9)	27% (12)
Risk communication		
Training	59% (21)	78% (25)
Health-care provider	60% (20)	69% (22)
Media	51% (19)	63% (22)
Public-health authority	52% (20)	63% (22)
Legal framework	23% (15)	38% (18)
Preferred minimal capacity		
Ability to link health-care databases	—	45% (14)
Ability to validate vaccine safety reports	—	36% (14)
Epidemiological studies	—	34% (11)

‡ Overall expressed needs were calculated for individuals: "yes" to the same item in either "existing programme" and "further needs" was counted as "yes" to the corresponding item in "overall expressed needs".

4.4 Need for international support

When describing elements of available infrastructures, 45% of professionals, coming from 18 countries, indicate that their countries rely partially on vaccine safety information from other countries (data not shown), and 30% of professionals, coming from 15 countries, wish to improve collaboration with other countries (Table 2). International support is needed for all scientific areas, emphasizing the need for training, particularly for concern investigation and risk communication (Figure 4, Table 2).

Figure 4: Perceived needs from international consortium, by area of activity



5. Discussion

This study was performed to assess the available capacity and expressed needs of vaccine safety monitoring in LMIC. It provides the most up-to-date summary of current opinions and expressed needs from a comprehensive sample of LMIC.

5.1 Importance of improving vaccine safety monitoring

Vaccine safety is of great concern in LMIC. The majority of professionals (96%) do not consider the current capacity to meet the needs in any of the four areas. This is particularly true for the functional aspects of the available infrastructure. Therefore, we suggest developing and implementing training modules for all areas of vaccine safety assessment, focussing on utilization of available infrastructure and building up of pharmacoepidemiologic capacity.

Most experts want to move beyond spontaneous reporting towards comprehensive systems to detect, verify, investigate and respond to vaccine safety concerns. In particular, methods for active surveillance (59%) based on health databases (55%) and guidance documents, are needed in the area of detection. For case verification, standardized case definition for outcomes (74%) and immunization records for exposure (63%), as well as expert committees for evaluation (73%), are needed. The main needs expressed for concern investigation, apart from training, include establishment of vaccine registries and secondary use of medical records in health databases. For risk communication, improvements should focus on public-health authorities (63%) utilizing public media (63%), and health-care providers (69%) listening to, and informing, their communities.

It is also important to regularly evaluate national capacity, especially the functional aspects of vaccine safety monitoring, in all four areas. This includes determination of criteria useful for evaluation of the investigational performance at national and international level. For example, the ability to detect concerns can be evaluated in several ways. An approach suggested would be to view detection systems as diagnostic tests, and to evaluate them according to generally-accepted test performance parameters, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and precision. This could be achieved by determining vaccine-event pairs, with true positive and true negative associations, as a benchmark.

5.2 Current infrastructure and functionality

Looking at structural elements alone, a high proportion of professionals indicated the readiness of their countries in monitoring the safety of vaccines. However, the consistent pattern of available infrastructure, lack of experience and common requirements for improvement, suggests that available infrastructures are less functional than desired. This may be explained by the relatively recent attention to developing vaccine safety systems. Thus, infrastructure is starting to be put in place, but there is still limited experience. Acquiring the experience necessary will undoubtedly require initial external support. The unequal ability to detect, investigate and respond to concerns in poor countries, also highlights the need to actively strengthen these countries according to a set of criteria for a minimal functional capacity.

5.3 Harmonized terminology and tools

The review of the responses received highlights the lack of a common language and also understanding of current concepts of vaccine safety monitoring in LMIC. For example, in the perception of experts there is a surprisingly high availability of advanced infrastructures, such as, to conduct active surveillance for concern detection, standard definition for case verification, vaccine registry and health-care databases. In addition to being an expression of the awareness of resources available potentially useful for vaccine safety monitoring, this is most likely due to different interpretations of terminologies. Another example is concern verification, which is reported by 56% professionals, from 22 countries, that have ever detected a concern, but only 33% professionals indicated the use of standardized case definitions. This implies that there might be differing concepts of case verification. This is further highlighted by the infrastructure reported from most professionals available for causality assessment. However, the assessment method reported is case-based causality assessment by experts. This is a process relying on the results of epidemiologic studies investigating associations, and mechanistic studies investigating the pathophysiology. Such studies appear to be only conducted in few countries; hence, there is a need for standardized terms and definitions and harmonized approaches shared by everyone contributing to a globally integrated vaccine safety monitoring system.

5.4 Information sharing and risk communication

Timely availability of pertinent data is an important characteristic of effective surveillance systems. Information sharing or data accessibility is critical for timely verification and causality assessment of vaccine safety concerns. There is a need for national legislation, and its effective implementation, to facilitate access to health-care databases and information from medical records for urgent public-health investigations.

Risk communication is among the weakest areas of vaccine safety monitoring in LMIC, both between agencies, and to the public. Professionals claim that availability of communication strategies is passively reacting to public questioning, at best. Given that 95% of professionals, from 23 countries, reported concern detection, and 82% professionals, from 20 countries, reported a negative impact on the immunization programmes and public confidence in immunization (data not shown), communication is an area which is in major need of improvement. It is of paramount importance to strengthen communication mechanisms in countries where the incidence of wild-type disease is high, and a decrease in the coverage rate based on insufficient monitoring and response systems poses an avoidable direct health risk to large parts of the population.

5.5 International support structure

The need for international support is expressed by the majority of professionals, 93% from 26 LMIC. The main needs identified are training, sharing of information, data, knowledge and technical support.

As a starting point for improving international collaboration, it is important to build consensus on a shared set of terms, concepts, definitions, guidelines, protocols and codes of conduct. Appropriate methodological and technical infrastructure and support for standardized data sharing and hypothesis testing at the global level is required.

The modes of interaction between national systems and a supranational infrastructure have to be established. Regular knowledge transfer and training would largely have to be coordinated and provided by regional or international organizations. For countries contributing to the global monitoring system, specialized support should be provided by rapid response teams.

5.6 Limitations

The main limitations of the study are the relatively small sample size, and possible information bias. Although the study randomly sampled experts to be contacted, engaging professionals who are in key positions in vaccine safety, and from different professions, in all countries to equal proportions, was a major challenge in this first attempt. Many professionals declined participation due to time constraints. In addition, different understandings of some questions could have partly resulted from country differences in use of terminology, or in culture, knowledge and experience.

6. Conclusions

There is a need expressed by LMIC experts to enhance vaccine safety monitoring, to improve verification of concerns based on international standards, to improve the infrastructure and analytical capacity for investigation of concerns, to promote information sharing between national organizations and across countries, to establish mechanisms and methods for risk communication and to establish training programmes and shared tools. These needs could best be accomplished through concerted effort and an international support structure so that countries can effectively perform vaccine safety functions. Follow-up studies are proposed to characterize specific baseline needs and to monitor progress made.

Appendix I : Cluster sampling of LMIC

Region	Sampling	LMIC		
		Low Income		
		Low population	Middle population	Large population
AFR	Selected	Gambia	Kenya	NA
	All in the cluster	Benin, Burundi, Central African Republic, Comoro,; Eritrea, Gambia, Guinea-Bissau, Liberia, Mauritania, Rwanda, Sierra Leone, Togo	Burkina Faso, Chad, Democratic Republic of the Congo, Ethiopia, Ghana, Guinea, Kenya, Madagascar, Malawi, Mali, Mozambique, Niger, Senegal, United Republic of Tanzania, Zambia, Zimbabwe, Uganda	NA
AMR	Selected	NA	Haiti	NA
	All in the cluster	NA	Haiti	NA
EMR	Selected	Somalia	Yemen	NA
	All in the cluster	Somalia	Afghanistan, Yemen	NA
EUR	Selected	Tajikistan	Uzbekistan	NA
	All in the cluster	Kyrgyzstan, Tajikistan	Uzbekistan	NA
SEAR	Selected	NA	Nepal	Bangladesh
	All in the cluster	NA	Myanmar, Nepal, Democratic People's Republic of Korea	Bangladesh
WPR	Selected	Lao People's Democratic Republic	Viet Nam	NA
	All in the cluster	Lao People's Democratic Republic	Cambodia, Viet Nam	NA
Region	**Sampling**	**Lower-middle income**		
		Low population	**Middle population**	**Large population**
AFR	Selected	Lesotho	Angola	Nigeria
	All in the cluster	Cape Verde, Congo, Lesotho, Sao Tome and Principe, Swaziland	Angola, Cameroon, Côte d'Ivoire	Nigeria
AMR	Selected	Paraguay	Ecuador	NA
	All in the cluster	Belize, Bolivia, El Salvador, Guyana, Honduras, Nicaragua, Paraguay	Ecuador, Guatemala	NA
EMR	Selected	Jordan	Egypt	Pakistan
	All in the cluster	Djibouti, Jordan	Egypt, Iran (Islamic Republic of), Iraq, Morocco, Sudan, Syrian Arab Republic, Tunisia	Pakistan
EUR	Selected	Georgia	Ukraine	NA
	All in the cluster	Albania, Armenia, Azerbaijan, Georgia, Kosovo, Republic of Moldova, Turkmenistan	Ukraine	NA
SEAR	Selected	Maldives	Sri Lanka	India
	All in the cluster	Bhutan, Maldives, Timor-Leste	Sri Lanka, Thailand	India, Indonesia
WPR	Selected	Mongolia	Philippines	China
	All in the cluster	Kiribati, Marshall Islands, Micronesia (Federated States of), Mongolia, Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu	Philippines	China

Appendix II: Definition of scientific areas of post-marketing vaccine safety monitoring

Concern detection (i.e. signal detection, signal generation) is defined as any genuine or alleged professional or public questioning related to the safety of a given vaccine or its associated programme. Passive surveillance is the collection of spontaneous adverse event following immunization (AEFI) reports, on a case-by-case basis, by medical care providers or laboratories for the local or national health agency. Active surveillance is the regular or proactive solicitation of adverse event reports, on a case-by-case basis, from health-care providers or facilities, for example, by regular distribution of reporting cards and active follow-up by a dedicated investigator.

Concern verification (i.e. signal strengthening) is the process to verify and strengthen a detected vaccine safety concern. It includes the act of verifying the relevant exposures and the outcome(s), as well as their known interactions.

Causality assessment (i.e. hypothesis testing, association studies, signal verification) is done by controlled epidemiologic studies to accept or reject a given null hypothesis. Hypothesis testing is different from causality assessment, which describes the process of determining etiologic and pathophysiologic evidence, for an event caused by immunization. This may be done on a case-by-case basis to make immediate decisions concerning the medical management. However, to generalize a causal relationship between immunization and a given health event, carefully designed epidemiological or laboratory experimental studies elucidating the aetiology and pathophysiologic mechanisms are required. Due to the different understanding of "causality assessment" reflected by the returned surveys, the term "concern investigation" is used to replace "causality assessment" in results presentation in this document.

Risk communication (i.e. inform public-health decision making, support public confidence) is the dissemination of information about the chance or likelihood that an undesirable health event will occur as a result of immunization. The aim is to improve understanding of vaccine profile, as well as evidence-based decision making, at both collective and individual levels. It also includes research into optimizing risk communication and adjusting the communication message for different target audiences.

Enhanced Strength-Weakness-Opportunity-Threat (SWOT+) Analysis Of International Vaccine Safety Activities (IVSA)

Executive summary

Within the framework of the WHO project developing a global vaccine safety strategy ("Global Vaccine Safety Blueprint") this study (Activity 1.2) investigated how international vaccine safety activities (IVSA) in the area of post-licensure vaccine safety monitoring can best serve the needs of a global vaccine safety programme.

The SWOT analysis was enriched by complementary questions (SWOT+) highlighting the qualitative characteristics of IVSA. Fifteen activities (Table 1) met the inclusion criteria (section 3.1). A comprehensive SWOT for each of the areas of vaccine safety monitoring highlighted increasing international collaboration as a core strength, and introduction of new vaccines in LMIC as a major opportunity. Evidence for unsustainable funding schemes and the lack of political support to build capacity and promote international collaboration, as major weaknesses and threats, is also provided (Tables 6, 7, 8, 9 and 10).

Furthermore, current services provided by IVSA at the global level were analysed to highlight gaps and potential synergies, redundancies and possible distribution of responsibilities among IVSA. All **areas** of vaccine safety monitoring are addressed by one or more IVSA (Table 2). However, there is a need for a strong coordinating infrastructure. The current focus is mainly on concern detection and validation (Table 3, Figure 1). A global strategy for building and utilizing health-care databases, as well as a central infrastructure for coordination, federation of databases, and data management and analysis is needed, to account for the gaps in reliably testing hypotheses and communicating risk (section 4.4.1). In addition, an integrated strategy should be built and implemented for communication between agencies, countries and IVSA.

In terms of shared **goals**, there is a high commitment to capacity building, innovation and development (Table 4, Figure 2). System evaluation is represented by only a few IVSA. The increased need for additional and trained staff in all areas highlights the need to establish and implement structured training and to sustain funding of IVSA. Limited resources highlight the need for the development and structured implementation of electronic tools, saving person time and thus improving current capacity needs specific to LMIC.

To move global safety monitoring to today's level of requirements, it is paramount to strengthen national-health systems to establish and maintain health-care databases and their secondary use for public health and research. International collaboration and strengthened global structures are essential to coordinate and support local vaccine safety activities. Current IVSA are in the position to provide the required services, pending sustainable funding and a global strategic plan guiding concerted action to achieve our common aims.

1. Rationale

Vaccine safety activities are important in all settings regardless of the income status. Although governments in developed economies have largely accepted and funded activities, LMIC have, in most cases, to rely financially and technically on global initiatives to establish an activity. However, there is only limited understanding of the impact of IVSA on the needs of LMIC. There is potential for optimizing and guiding concerted international collaboration to achieve common aims.

The development of a global blueprint for vaccine safety monitoring by the World Health Organisation, with funding from the Bill & Melinda Gates Foundation, will permit harmonization of IVSA by describing strategic plans, budget and funding options, and governance principles of a globally integrated vaccine safety consortium. It is based on a structured analysis of vaccine safety monitoring infrastructure (Activities 1.1 to 1.7) with particular focus on LMIC, of which the current study is an integral part.

2. Goals

Within the framework of developing the blueprint, this study (Activity 1.2) aims to describe how established IVSA can best serve the needs of a global vaccine safety programme, and also to propose roles and responsibilities.

3. SWOT analysis design

A SWOT analysis is enriched by complementary questions (SWOT+) guiding harmonization and capacity building at the global level. For the purpose of this SWOT+, the following definitions of terms apply.

- Activity is used synonymously for any project, initiative, commitment or dedicated action in the field of post-marketing vaccine safety, with an international scope and a track record of at least one year, and visible outcomes.
- Strengths are defined as internal capabilities to reach a specific goal, e.g. experienced staff, necessary infrastructure.
- Weaknesses are defined as internal deficiencies to reach a specific goal, e.g. rigid organizational structure, lack of trained staff.
- Opportunities are defined as external factors that positively influence an activity to reach a goal, e.g. political/ legal support.
- Threats are defined as external factors negatively influencing an activity to reach a goal, e.g. economic crises, adverse media attention.

3.1 Selection of IVSA

The Collaborative Group defined the requirements and characteristics of an IVSA during two retreats (9–11 February 2010, Geneva, and 6–8 July 2010, London). IVSA were characterized and defined by:

- having international scope (i.e. involving more than one country);
- a track record of activity for at least one year (i.e. implementation, not planning phase);

- concerned with post-licensure vaccine safety monitoring;
- advocating vaccine safety (i.e. recognizing the public-health benefit of vaccines and contributing to the evaluation of their risk-benefit profile);
- being recognized by the Brighton Collaboration as a resource of trusted information and support (i.e. activities with a track record of high-quality scientific information);
- being respected as a trusted consultant by regional, national and international monitoring systems (i.e. activities with a track record of consultations deemed useful by the beneficiaries).

IVSA are identified based on Activity 1.1 of the Global Blueprint and selected by the Collaborative Group based on the predefined criteria outlined above.

4. Results

Fifteen IVSA met the inclusion criteria (Table 1). Several additional activities concerned with post-licensure vaccine safety monitoring were initially identified for evaluation, or proposed for inclusion via the stakeholder survey (Activity 1.1 of the Global Blueprint). However, they were either one-time projects or meetings, or not international in scope. From the IVSA included, we received completed questionnaires from all 15 participants (100% return rate).

Table 1: Fifteen activities were selected by the Collaborative Group during the London retreat 6–8 July 2010

Nr	Activity	Lead organization
1	WHO Programme for International Drug Monitoring – the Uppsala Monitoring Centre (UMC)	WHO – UMC
2	Post-marketing surveillance network of recently prequalified vaccines (PMS Net)	WHO
3	National regulatory authority assessment (NRA)	WHO
4	Vaccine safety training programmes (VS training)	WHO – IVB, GACVS
5	Developing Countries' Vaccines Regulators Network (DCVRN)	WHO
6	Council for International Organization of Medical Science (CIOMS) and WHO working group on vaccine pharmacovigilance	CIOMS – WHO
7	Case definitions, guidelines, protocols for standardized verification of adverse events (standards – BC)	BC
8	Automatic case verification (ABC – BC)	BC
9	Global vaccine safety data link (GVSD) – background rates for concern verification (BGR – BC)	BC
10	Vaccine safety crisis management/rapid response team	WHO – UMC
11	GVSD – hypothesis-testing studies	BC
12	Global Advisory Committee on Vaccine Safety concerns (GACVS)	WHO
13	Building public confidence/rumour surveillance project	LSHTM
14	Vaccine safety concern response and consultancy service	CDC (USA)
15	International collaborative vaccine safety consortium (WHO/FDA)	WHO – FDA

4.1 Regions

Most IVSA support all WHO regions. The DCVRN is not active in the WHO European Region. Together with its partners, the BC has built methodological and technical infrastructure for international collaborative studies in Europe. While the CDC International Standards Organization (ISO) has provided international consultancy services for more than a decade to surveillance systems on all continents, the group is currently reforming and defining its new direction and scope.

4.2 Summarized services

In general, all areas of vaccine safety monitoring are addressed by one or more IVSA (Table 2). The approach by each activity taken to address the goals in the respective areas varies, and is analysed in more detail in the sections below. The key questions to be addressed are, uniqueness versus redundancy of activities performed by IVSA, as well as the degree to which IVSA addresses local needs.

Table 2: Summarized services (✓= actually being performed)

		AREAS			
		Concern detection	**Concern validation**	**Hypothesis testing**	**Risk communication**
GOALS	Providing and communicating evidence	✓	✓	✓	✓
	Innovation, development	✓	✓	✓	✓
	Capacity building	✓	✓	✓	✓
	System evaluation	✓	✓	✓	✓

4.3 IVSA by area

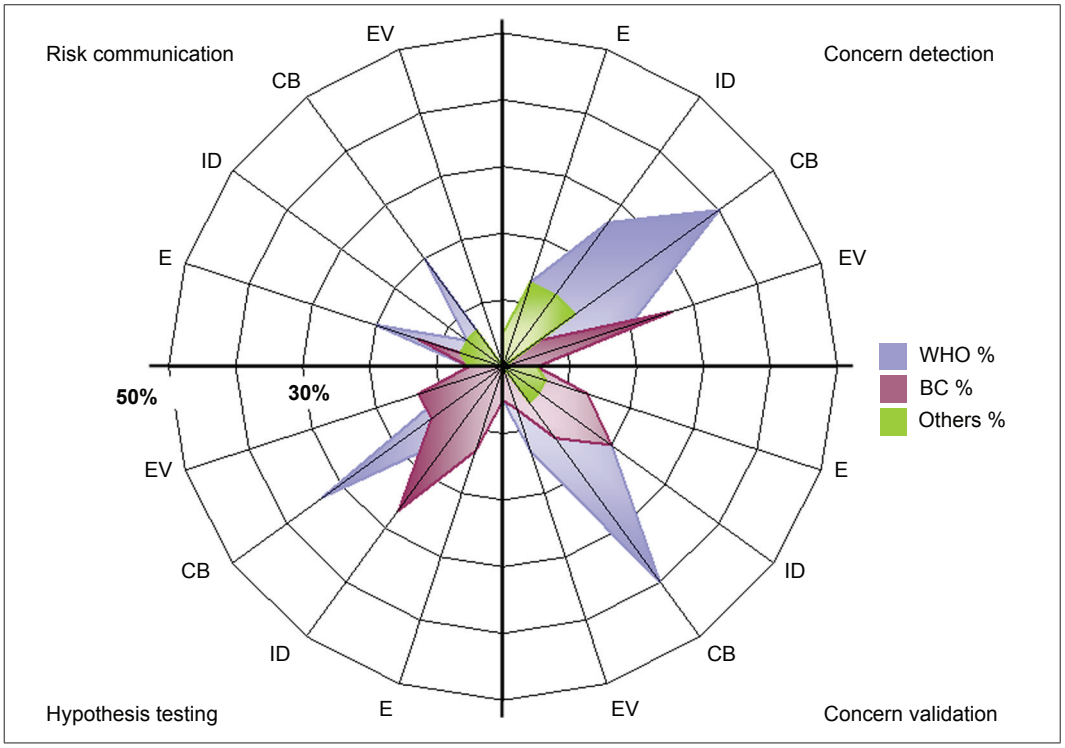
IVSA provide services at the national level, towards specific goals, in the areas outlined in Table 3. There is an uneven distribution of IVSA across the different areas. Representation is decreasing, from concern detection, to concern validation, to hypothesis testing, to risk communication. This is not only true for the areas, but also for the goals within the areas; decreasing from providing evidence, to innovation and development, to capacity building and system evaluation. Overall, risk communication appears to be the area least represented (Figure 1).

Table 3: Services provided in the different areas by activity; (E = providing and communicating evidence; ID = innovation, development; CB = capacity building; EV = system evaluation)

		Concern detection				Concern validation				Hypothesis testing				Risk communication			
		E	ID	CB	EV	E	ID	CB	EV	E	ID	CB	EV	E	ID	CB	EV
1	UMC – WHO	■	■	■				■									
2	PMS Net – WHO		■	■	■			■									
3	NRA – WHO		■	■	■		■	■	■							■	
4	VS training – WHO			■				■				■				■	
5	DCVRN – WHO											■					
6	CIOMS – WHO						■										
7	Case definitions & guidelines – BC		■	■	■	■	■	■			■						
8	ABC – BC				■		■				■						
9	BGR – BC				■	■	■	■		■	■	■	■	■			
10	VS crisis management – WHO	■	■	■		■	■	■			■	■		■	■		
11	Hypothesis-testing – BC				■				■	■	■	■	■	■			
12	GACVS – WHO			■	■	■		■	■			■	■	■		■	
13	Public confidence – LSHTM	■	■	■										■	■	■	
14	VS response – CDC	■	■	■		■	■	■									
15	International VS consortium – FDA/WHO									■	■	■		■			
	Number	4	7	9	7	5	7	9	3	3	6	7	3	6	2	4	0
	% of IVSA	27	47	60	47	33	47	60	20	20	40	47	20	40	13	27	0
	% of all services	5	9	11	9	6	9	11	4	4	7	9	4	7	2	5	0
	TOTAL %	33				29				23				15			

Figure 1 highlights the findings shown in Table 3 by visualizing the pattern of distribution of IVSA in the various areas and goals. This figure allows rapid assessment of the current situation, and facilitates evaluation of the impact of a global vaccine safety programme. It can guide strategic planning by identifying areas of over and under representation. For example, the decreasing representation of detection>validation>testing> communication can be easily appreciated from this graph. Figure 1 further dissects areas of over and under representation by highlighting areas of potential overlap between IVSA when grouped by organization. Whether this represents duplication of organizational strategy, or the opportunity for synergistic interaction, is further elaborated in the sections below. For example, the involvement of WHO and the Brighton Collaboration in concern detection, validation and testing has different synergistic emphases. While WHO is focusing more on capacity building, the BC is focusing more on system evaluation as part of concern detection and innovation, and development as part of validation and hypothesis-testing.

Figure 1: Distribution of groups of IVSA (WHO, BC, others = LSHTM, USCDC) by areas and goals; (E = providing and communicating evidence, ID = innovation, development, CB = capacity building, EV = system evaluation)



4.4 IVSA by goals

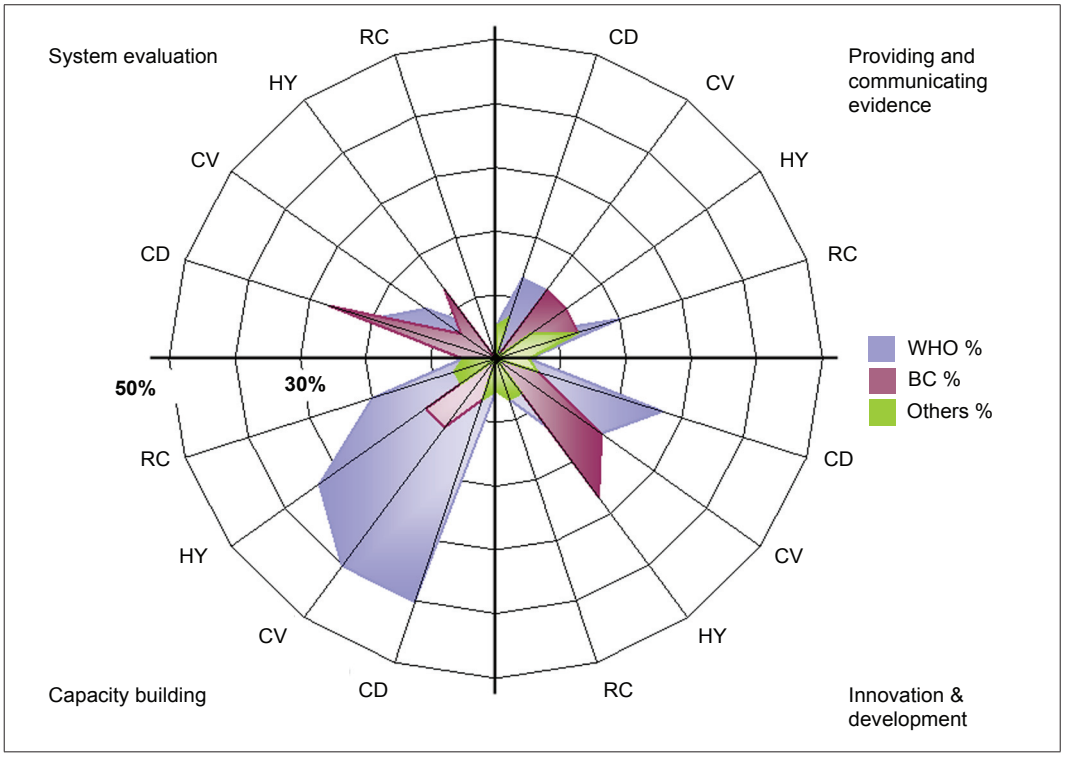
IVSA provide services at the national level towards specific areas in the following goals (Table 4). In general, there is a high commitment towards capacity building, and innovation and development. Systematic evaluation of hypothesis testing and risk-communication activities seem to be represented only by a few IVSA (Figure 2).

Table 4: Services provided in the different goals by activity; (CD = concern detection, CV = concern validation, HY = hypothesis testing, RC = risk communication)

		Providing and communicating evidence				Innovation, development				Capacity building				System evaluation			
		CD	CV	HY	RC	CD	CV	HY	RC	CD	CV	HY	RC	CD	CV	HY	RC
1	UMC – WHO	■				■				■	■						
2	PMS Net – WHO					■				■	■			■			
3	NRA – WHO					■	■			■	■		■	■	■		
4	VS training – WHO									■	■	■	■				
5	DCVRN – WHO											■					
6	CIOMS – WHO						■										
7	Case definitions & guidelines – BC		■			■	■	■		■	■			■			
8	ABC – BC						■	■						■			
9	BGR – BC		■	■	■		■	■			■	■		■		■	
10	VS crisis management – WHO	■	■		■	■	■	■	■	■	■	■					
11	Hypothesis testing – BC			■	■			■				■		■	■	■	
12	GACVS – WHO		■		■					■	■	■	■	■	■	■	
13	Public confidence – LSHTM	■			■	■			■	■			■				
14	VS response – CDC	■	■			■	■			■	■						
15	International VS consortium – FDA/WHO			■	■			■				■					
	Number	4	5	3	6	7	7	6	2	9	9	7	4	7	3	3	0
	% of IVSA	27	33	20	40	47	47	40	13	60	60	47	27	47	20	20	0
	% of all services	5	6	4	7	9	9	7	2	11	11	9	5	9	4	4	0
	TOTAL %	18				22				29				13			

Figure 2 highlights the findings shown in Table 4 by visualizing the pattern of IVSA involvement in the various areas and goals. This figure allows rapid assessment of the current situation, and also the evaluation of the impact of a global vaccine safety programme. It will guide strategic planning by identification of areas of over and under representation. Figure 2 further dissects areas of over and under representation by highlighting potential overlap. Whether this represents duplication of work or the opportunity for synergistic interaction is further elaborated in the sections below. For example, WHO is by far the strongest capacity builder and is developing spontaneous reporting systems through several IVSA. The BC is strong in innovation and development for hypothesis testing studies and case verification, as well as system evaluation for concern detection and hypothesis testing. Only a few IVSA provide and communicate evidence. This probably reflects that data are primarily generated at national level and by specific research groups, and indicates an opportunity for internationally coordinated efforts in this area.

Figure 2: Distribution of groups of IVSA (WHO, BC, others = LSHTM, USCDC) by areas and goals; (CD = concern detection, CV = concern validation, HY = hypothesis testing, RC = risk communication)



The sections below further crystallize how capacity is built and what exactly each IVSA has innovated and developed. The goals of providing and communicating evidence, as well as system evaluation, are not specified, as instructive details of how the respective goal is achieved were not solicited.

Training and consultancy are dominant, and equally represented in capacity building. Providing funding, infrastructure and educational material are comparatively underrepresented. In addition, international consensus is needed on the delineation of consultancy services and training.

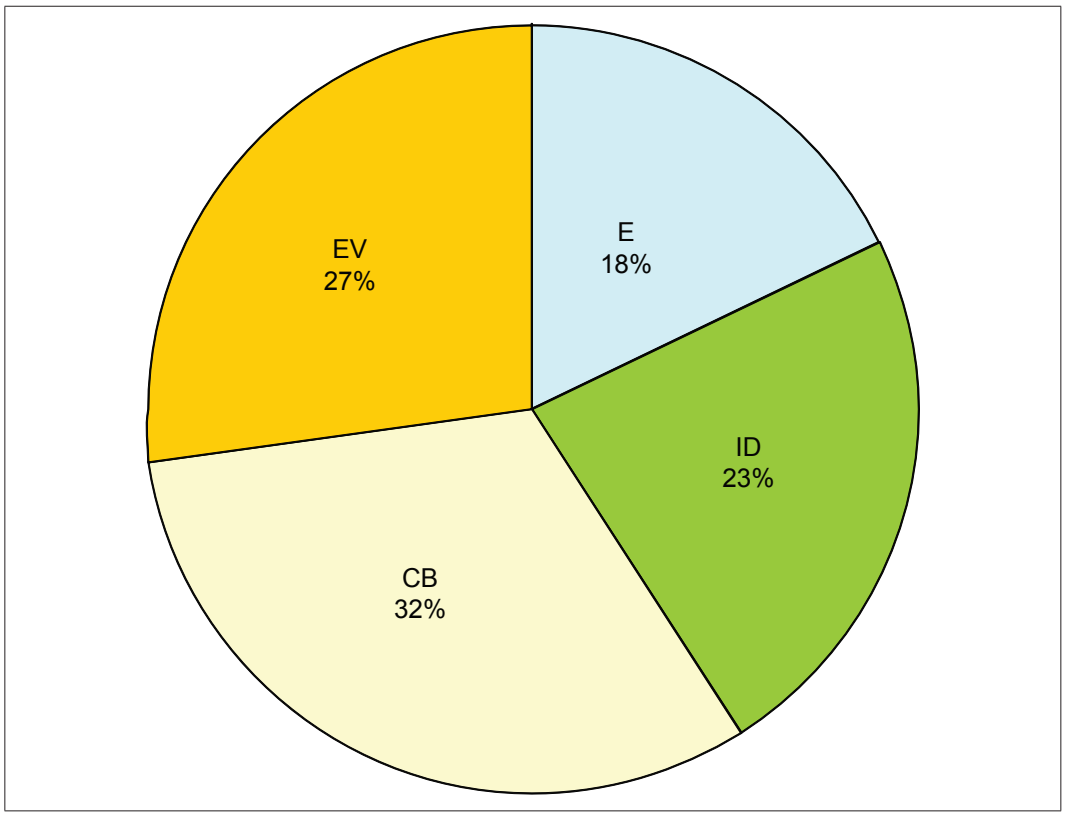
There is an almost equal distribution between tools, standards and policies in innovation and development. While this distribution appears reasonable, it might be argued that policy and recommendations are functionally closer to consultancies as part of capacity building, rather than actual innovations.

4.4.1 Linkage of health-care databases

Several IVSA are dedicated to promoting the availability and use of health-care databases for vaccine safety monitoring. There are three main elements: (1) outcome databases (OD), including disease/death databases and hospital records; (2) exposure databases (ED), including immunization databases; (3) national unique patient identifiers (UI). Figure 3 shows the respective involvement of IVSA in providing and communicating evidence (e.g. data generation), innovation and development (e.g. electronic tools), capacity building (e.g. infrastructure for international data sharing) and system

evaluation (e.g. quality assurance) of these main elements. Seven out of 15 IVSA indicated providing provision for health-care database services. Overall, IVSA are most active in the area of capacity building (32%), followed by providing and communicating evidence about baseline data (27%), innovating and developing methods and tools for the generation and management of vaccine safety data from health-care databases (23%), and the evaluation of health-care databases (18%) (Figure 3). Thirty per cent of IVSA services focus on exposure databases and 70% on outcome databases. No activity explicitly targets the establishment of national unique patient identifier systems.

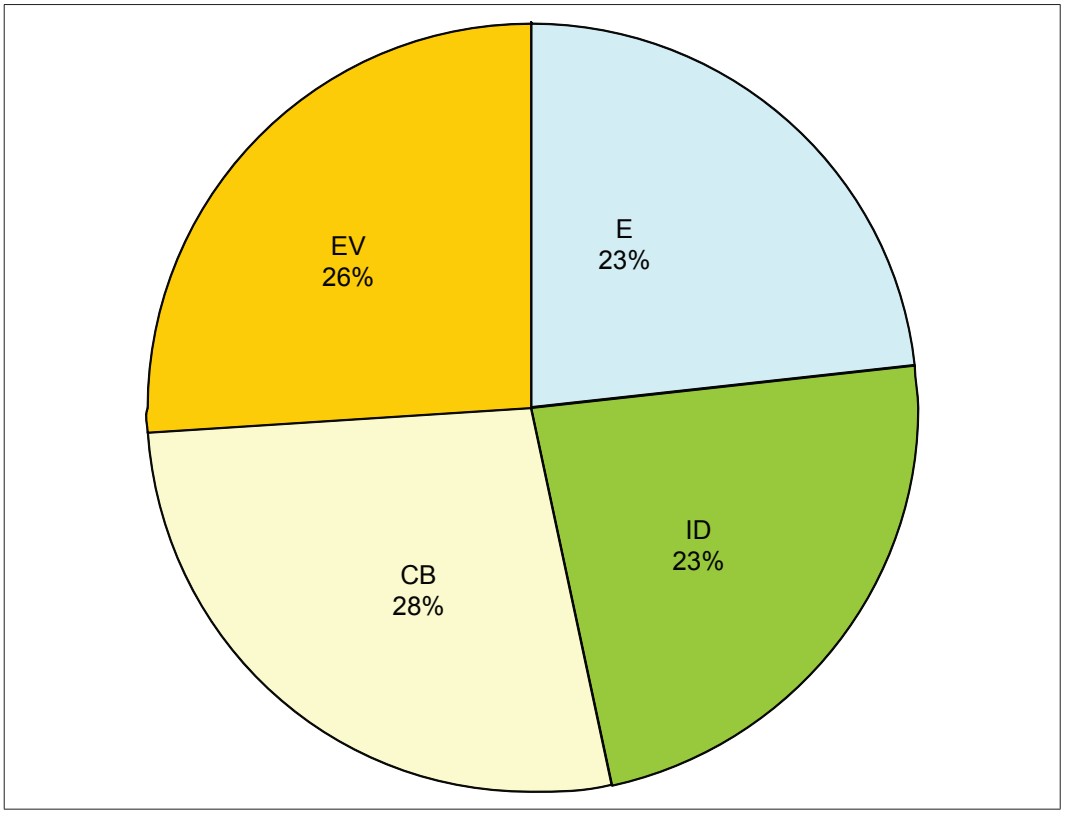
Figure 3: Distribution of linkage of health-care database services (i.e. OD, ED, UI) by goals; (E = providing and communicating evidence, ID = innovation, development, CB = capacity building, EV = system evaluation)



4.4.2 Enabling services

Regional sharing of data and other information, political recognition, legal frameworks and public perception, and beliefs in vaccine safety are the key elements of enabling services. Eleven out of 15 IVSA are active in enabling services. Overall, IVSA focus on the areas of capacity building (CB) for enabling services (28%), followed by the evaluation of data-sharing systems, political recognition, the legal framework or public perception (26%) and providing and communicating evidence (E) (23%), and innovating and developing methods and tools (ID) (23%) (Figure 4). IVSA provide 40% of services enabling regional data sharing, 30% targeting public perception, 26% eliciting political recognition and 4% providing a legal framework.

Figure 4: Distribution of enabling services by goals; providing and communicating evidence (E), innovation, development (ID), capacity building (CB), system evaluation (EV)



4.5 Staff in IVSA

Table 5 gives an overview of the current situation and 5-year development plan of teams by IVSA (0.9 = 90%, 1 = 100% time job). The overall distribution of scientific, coordinative and administrative full time equivalents (FTEs) is 61%, 27% and 12%, respectively. The number of staff engaged in WHO NRA assessment (16) is an outlier and refers to regional office staff. Other activities are more centrally organized and engage only a fraction of staff, with 1–2 FTE. On an organizational level, most FTE are located at WHO (n=28) — even after possible modification of the staff assigned to NRA assessment (n=13). Currently, CDC has no personnel assigned to IVSA, due to current internal reorganization. Apparently, 10 FTE are planned at CDC. The total planned FTE foresees an increase of about 80% (21 FTE) within the next five years. The overall distribution of scientific, coordinative, and administrative FTEs is 56%, 26% and 18%, respectively. Thus, a disproportional increase of administrative FTEs is planned. Of the 21 planned FTE, 10 are envisioned by, and at, CDC, five by BC, four by WHO and two by others.

Table 5: Distribution of staff engaged in IVSA; (SMC = scientific, medical or communication, C = coordination, A = administrative, * = TBD, ** = NA, v = volunteers)

ID	Name	Actual FTE				Planned FTE			
		SMC	C	A	Total	SMC	C	A	Total
1	UMC – WHO	0.9	0.1	0	1	1.2	0.1	0	1.3
2	PMS Net – WHO	1.6	0.2	0.1	1.9	*	*	*	0
3	NRA – WHO	3	0.75	0.6	4.3	3	0.75	0.6	4.3
4	VS training – WHO	**	**	**	0	2	0.5	1.5	4
5	DCVRN – WHO	0	1	0	1	0	1	0	1
6	CIOMS – WHO	1.25	0.1	0.1	1.4	*	*	*	0
7	Case definitions & guidelines – BC	0.5	0.5	0.2	1.2	2	1	0.2	3.2
8	ABC – BC	0.5	0.2	0.2	0.9	0.5	0.5	0.2	1.2
9	BGR – BC	0.5	0.5	0.2	1.2	1	0.5	0.4	1.9
10	VS crisis management – WHO	2.75	0.1	0.4	3.25	4.5	0.2	0.8	5.5
11	Hypothesis testing – BC	0.5	0.5	0.2	1.2	1.5	1.5	1	4
12	GACVS – WHO	0.7	0.5	0.5	1.7	0.7	0.5	1	2.2
13	Public confidence – LSHTM	4.6	2	0.5	7.1	5.6	2.5	1.5	9.6
14	VS response – CDC	0.05	0.1	–	0.2	5.6	2.5	1.5	9.6
15	International VS consortium – FDA/ WHO	v	1	0.2	1.2	v	1.1	0.2	1.25
	Total WHO	10.2	3.7	1.9	15.8	11.4	4.1	4.1	19.6
	Total BC	2.0	1.7	0.8	4.5	5.0	3.5	1.8	10.3
	Total others	4.7	2.1	0.5	7.2	11.2	5.0	3.0	19.2
	Total per type of staff	16.9	7.5	3.2	27.5	27.6	12.6	8.9	49.1

4.6 Analysis of weaknesses and threats

Table 6 shows the results of the analysis of weaknesses and threats mentioned by the IVSA. Thirteen out of 15 IVSA mentioned that the soft and unsustainable funding bases of their activities were the biggest threat. The lack of funds and the reliability on soft money is directly influencing manpower and expertise (11 out of 15 IVSA).

Table 6: Analysis of weaknesses and threats mentioned by the IVSA

		No of IVSA
1.	Soft, unsustainable funding	13
2.	Expertise and manpower	11
3.	Methods, data, timeliness CD, CV, HY, RC	5
4.	Advocacy, willingness, commitment	4
5.	Global shared strategic plan, SOPs	3
6.	Lack of national immunization programme involvement in PMS	1
7.	Lack of collaboration between NRA and MOH (NIP)	
8.	Collaboration with other organizations	1
9.	Certification and monitoring system (evaluation systems)	1
10.	Geographical distribution	1

4.6.1 Concern detection

Table 7: SWOT analysis for the area concern detection

Strengths	Weaknesses
• Globally centralized reporting system with standard report form • Global database of spontaneous AEFI reports • Interactive network established • WHO is highly trusted coordination and evaluation hub • Influencing local decision making • Strong international technical expertise • Established training programmes • System or signal evaluation in place	• Soft, unsustainable funding at the international level • Lack of human resources • Slow implementation of funds • Lack of national immunization programme involvement in PMS • Lack of collaboration between NRA and MOH (NIP) • Lack of training and advocacy • Training demand exceeds WHO capacity • Limited collaboration with organisations that have training capacity • Lack of international data-exchange agreements
Opportunities	**Threats**
• Increasing electronic infrastructure in LMIC • Increasing recognition of importance in LMIC • Increasing general investment in LMIC health systems • Network expansion • Recognized need for training	• Consequences of soft, unsustainable funding • Loss of centralized coordination • Lack of institutional development process for post-marketing surveillance

4.6.2 Concern validation

Table 8: SWOT analysis for the area concern validation

Strengths	Weaknesses
• Broad stakeholder representation • Strong methodological expertise • Dedicated and large global network of experts • Highly cost effective • Automated validation tools • Rapid-response teams for concern validation can be built • Expert committee evaluating concerns	• Lack of funds • Lack of central coordinating staff • Low LMIC representation • Delayed dissemination and implementation • Limited availability and timely deployment of rapid-response teams for concern validation • Lack of standard operating procedures for concern validation by rapid-response teams
Opportunities	**Threats**
• Increasing recognition of the need in LMIC • Increasing numbers of vaccine safety crises • Increasing investment in safety surveillance infrastructure • Increasing need for global collaboration	• Consequences of soft, unsustainable funding • The lack of willingness to update current systems to reflect shared standards • Lack of collaboration between NRA and MOH • Lack of international data-exchange agreements

4.6.3 Hypothesis testing

Table 9: SWOT analysis for the area hypothesis testing

Strengths	Weaknesses
• Dedicated and large network • Simple, flexible and elegant infrastructure for data management, transfer and analysis • Active knowledge transfer to LMIC • Internationally shared protocols for various study designs available • Liaisons with local researchers, institutions and hospitals • Flexible participation requirement depending on national resources • Expert committee reviewing hypothesis testing results	• Lack of funds for study coordination and conduct • Lack of electronic health records and immunization registries in LMIC • Lack of international data-exchange agreements
Opportunities	**Threats**
• Increasing availability of electronic health records and immunization registries in LMIC	• Lack of political willingness and public-health priority

4.6.4 Risk communication

Table 10: SWOT analysis for the area risk communication

Strengths	Weaknesses
• Global advisory committee in place (GACVS) • International advisory group, focus on LMIC • Tools in development	• Soft, unsustainable funding at the international level • Lack of international data-exchange agreements • Lack of staff and widely shared expertise
Opportunities	**Threats**
• Most underdeveloped area • Increasing recognition of importance	• Consequences of soft, unsustainable funding

5. Discussion

In the framework of the WHO project developing a global vaccine safety strategy, this study (Activity 1.2) describes how established IVSA can best serve the needs of a GLOBAL VACCINE SAFETY PROGRAMME and proposes roles and responsibilities.

We believe that this is the first SWOT analysis of IVSA. The SWOT analysis was enriched by complementary questions (**SWOT+**) guiding harmonization and capacity building at the global level. The SWOT analysis highlights the *qualitative characteristics of the individual IVSA*. These characteristics are unique to each IVSA and cannot usefully be compared analytically. However, to guide the development of the global vaccine safety strategy, we have standardized the individual services and summarized the collective strengths, weaknesses, opportunities and threats by area of vaccine safety monitoring (Tables 6, 7, 8, 9 and 10). The SWOT has provided individual IVSA profiles (available in the full report) which may be utilized for identification of potential redundancies, synergies and distribution of responsibilities among IVSA. The SWOT analysis has highlighted that increasing *international collaboration and networking* are perceived as strengths in all areas. The increasing *introduction of new vaccines in LMIC* is seen as a major opportunity to foster international collaboration among most of the IVSA in all areas. *Unsustainable funding schemes and the lack of political willingness* to build capacity and promote international collaboration are perceived as the major threats to addressing apparent needs. The lack of trained staff in all areas, not only at the national but also at the international level, highlights the need to *establish and implement structured training*.

To illustrate the *number and relative distribution of IVSA* across the different areas and goals of vaccine safety monitoring, we have employed **spider-web graphs**. They neither inform about the quality of the work performed, nor do they highlight an implied need by the area not covered, but show the pattern of distribution visualizing the numbers of IVSA addressing the various areas and goals of vaccine safety monitoring. This can be used as a tool to inform strategic planning, by streamlining and prioritizing current activities as well as identifying potential gaps.

In general, all areas of vaccine safety monitoring, including concern detection, validation, hypothesis testing and risk communication, as well as enabling services, *are addressed* by one or more IVSA. Thus, at the international level, there is awareness of all areas of vaccine safety monitoring relevant to LMIC, and the basic resources to provide some of the services required (Table 2). However, there is a need for streamlining the current activities, fostering expansion, in the light of increasing demand from LMIC, and also well concerted global collaboration. Therefore, *a strong coordinating infrastructure is needed at the global level*.

The different **areas** of vaccine safety monitoring are not equally addressed by the IVSA. The current focus is mainly on concern detection and validation (Figure 1). Most IVSA have highlighted the increased need for a robust vaccine safety monitoring infrastructure due to increased development and marketing of vaccines in LMIC. This involves reliable hypothesis testing and risk- communication capacity. There are currently two IVSA actively addressing this need; The International Collaborative Vaccine Safety Consortium and the Brighton Collaboration Global Vaccine Safety Datalink. A global strategy for *building and utilizing health-care databases, as well as a central infrastructure for coordination, federation of databases, and data management and analysis, is needed*. Only one IVSA is exclusively dedicated to risk communication; building public confidence – rumour surveillance project. In concert with other IVSA significantly involved in risk communication, *an integrated strategy for communication between agencies, countries and IVSA should be built and implemented*.

In terms of **goals**, there is a high commitment to capacity building, and innovation and development (Table 4). System evaluation seems to be represented only by few IVSA (Figure 2). This appears to be a reasonable distribution, given that capacity building and innovation in the various areas requires highly specialized expertise and benefits from well-coordinated interaction of multiple partners. On the other hand, system evaluation may benefit more from a highly centralized and conceptualized approach. As the global umbrella of public-health organizations involved in vaccine safety, as well as national immunization programmes, the WHO appears to be most suited to oversee system evaluation and quality control. WHO NRA assessments have extensive and unique experience in evaluating spontaneous reporting systems. Subject-matter expertise on other vaccine safety areas should be provided to WHO by the respective IVSA.

For **capacity building**, training and consultancies are the focus of current activities. Whether consultancies are considered as capacity building or as an integral part of providing any service, is a matter of consensus on classification. For future use of our proposed SWOT+ approach to monitor and evaluate vaccine safety services available and capacity at the international level, we propose to build consensus on a shared *glossary* of terms utilized and understood by all stakeholders in the field. Such a glossary would comprise, for future reference, a comprehensive set of technical terms related to post-marketing vaccine safety monitoring.

Similarly, the need for *educational materials and structured training* overwhelms current capacity. Therefore, modules and a content syllabus for comprehensive vaccine safety training delivered by the various IVSA in their respective areas of expertise, as well as by public health, academic, and private market training institutions, should be developed and implemented. We consider consultancies to rarely represent structured training. Thus, we would recommend classifying consultancies as being directly linked to providing and communicating evidence.

Providing *funding and building infrastructure* are the most obvious services to directly build capacity. Both are comparatively underrepresented. Given the increasing impact of safety concerns on global health, the fact that most work is based on time restricted "soft money" we believe to be irresponsible.

Apart from training of current staff at the international level, there is an increased *need for additional staff*, given the increasing need for globally concerted action. An increase of about 80% (21 FTE) is anticipated in the next five years, and will involve scientific, coordinating and administrative personnel (Table 5). Given the public-health importance of vaccine safety and the extensive work done on an international level, *the number of staff involved is marginal*. The most cost effective and flexible engagement of this additional workforce should be considered. This will require significant direct and sustainable funding.

In terms of infrastructure, the limited resources highlight the need for the development and structured implementation of *electronic tools saving person time and addressing current shortcomings and issues specific to LMIC*, while improving timely availability of high quality and comparable vaccine safety information. To move global safety monitoring to today's requirement levels, serious investment is paramount in strengthening national health systems, to *establish and maintain health databases* and their secondary use for public health and research. The availability of international infrastructures and simple electronic tools, plus established methodologies and successful proof of principle studies should meet the current efforts in LMIC building electronic health databases.

6. Conclusions

Never before has there been a better opportunity to utilize national and international strengths to meet the increasing need of robust vaccine safety monitoring and research in LMIC. There is international awareness of this need. The components necessary to build sustainable vaccine safety monitoring in LMIC are known. Highly-specified vaccine safety expertise, and vast experience, is available at a global level. Health-care capacity is being built in LMIC. The time is right to leverage international expertise and promote international collaboration to strengthen national vaccine safety monitoring and international sharing of vaccine safety data. The currently available IVSA are in the position to provide the required services, pending a sustainable funding base and a global strategic plan.

Appendix: Glossary

Concern detection (i.e. signal detection, signal generation) is defined as any genuine or alleged professional or public questioning related to the safety of a given vaccine or its associated programme. Passive surveillance is the collection of spontaneous AEFI reports on a case-by-case basis by medical care providers or laboratories to the local or national health agency. Active surveillance is the regular or proactive solicitation of adverse event reports on a case-by-case basis from health-care providers or facilities, for example, by regular distribution of reporting cards and the active follow-up by a dedicated investigator.

Concern validation (i.e. signal strengthening) is the process to verify and strengthen a detected vaccine safety concern. It includes the act of verifying the relevant exposures and the outcome(s), as well as their known interactions.

Hypothesis testing (i.e. association studies, signal verification) is done by controlled epidemiologic studies to accept or reject a given null hypothesis. Hypothesis testing is different from *causality assessment* which describes the process of determining etiologic and pathophysiologic evidence for an event to be caused by immunization. This may be done on a case-by-case basis to make immediate decisions concerning the medical management. However, to generalize a causal relationship between immunization and a given health event, carefully designed epidemiological or laboratory experimental studies are required elucidating the aetiology and pathophysiologic mechanisms.

Risk communication (i.e. inform public-health decision making, support public confidence) is the dissemination of information about the chance or likelihood that an undesirable health event will occur as a result of immunization. The aim is to improve understanding of vaccine profile, as well as evidence-based decision making, at both collective and individual levels. It also includes research into optimizing risk communication and adjusting the communication message for different target audiences.

Providing and communicating evidence is the goal of IVSA situated at the frontline of vaccine safety monitoring, by actively detecting concerns (e.g. signal detection, signal generation), actively validating concerns, actively testing safety hypothesis, or communicating risks. It is also the goal of IVSA responding with scientific rigour to vaccine safety issues of potential global importance.

Innovating or developing standards, methods or tools is the goal of IVSA supporting monitoring, research or communication systems to improve concern detection, concern validation, hypothesis testing, or risk communication.

Capacity building is the goal of IVSA supporting monitoring, research or communication systems to better detect concerns, validate concerns, test hypotheses, or communicate risks.

System evaluation is the goal of IVSA supporting concern detection, concern validation, hypothesis testing, or risk communication systems, by evaluating and consulting for improvement.

Survey of regulators

1. Introduction

The perspectives of regulatory licensing authorities were assessed in countries that produce, procure, and both produce and procure vaccines. A web-based survey was developed to explore regulators' knowledge, attitudes and practices concerning their national vaccine safety system. Additionally, their opinions about what would be needed to ensure future capacity and capabilities for a global vaccine safety system were probed, along with models of collaboration for regulatory authorities and the private sector that address public safety issues.

This survey addressed four key objectives.

- To assess knowledge, attitudes and practices of low- and middle-income country vaccine safety systems from the perspective of licensing authorities in (a) producing, and (b) procuring countries.
- To assess expectations of (a) producing, and (b) procuring countries, regarding a global vaccine safety system, in order to provide information essential to formulate the blueprint.
- To assess the understanding of minimal capacity (from high- middle- and low-income country regulators) for ensuring vaccine safety in their countries.
- To assess existing models of collaboration between regulatory authorities with industry (in high- middle- and low-income countries).

2. Description of methods

A sample frame of low- middle- and high-income countries with a range of population sizes, across WHO regions, was developed to meet the following inclusion criteria:

- countries that produce, procure, and both produce and procure vaccines;
- representation of all WHO regions (AFR, AMR, SEAR, EUR, EMR, WPR);
- representation of World Bank categories for high- middle- and low-income countries;
- representation of countries from three population size categories: < 40 million, 40–80 million, > 80 million.

The survey was sent to regulators in 32 countries and made available in English, French, Spanish and Russian versions. Responses were received from 19 countries and, additionally, a survey was completed by the European Medicines Agency (Table 1).

There was intentional overrepresentation of low- and middle-income countries in the sample frame, in order to capture data most relevant to the goals of the blueprint project. The WHO Region of the Americas was overrepresented to accommodate existing surveillance initiatives. Representation across all categories except one (we were unable to recruit a middle sized low-income country) was attained. We augmented our study findings by asking the European Medicines Agency (EMA) to complete the survey. The EMA takes into consideration issues representative of 27 Member countries of varying size and income, including the three European Region countries who independently responded to our survey. In all, data from three African Region, six Region of the Americas, three South-East Asia Region, three European Region, two Eastern Mediterranean Region and two Western Pacific Region countries were included in the survey. There was a final response rate of 59.4% (19 responding countries of 32 contacted). In total, data from 20 surveys (19 plus the EMA) were included in the analysis of this report. Overall, the actual survey sample provides good country representativeness.

Table 1: Survey sample frame

	Population < 40m	Population 40–80m	Population > 80m
High	4 of 5 (1 procuring, 1 producing and 2 producing and procuring countries)	1 of 1 (producing country)	1 of 1 (producing country)
Middle	4 of 10 (3 procuring and 1 producing and procuring countries)	2 of 2 (both producing and procuring countries)	4 of 8 (1 procuring and 3 producing and procuring countries)
Low	2 of 3 (2 procuring countries)	0 of 1	1 of 1 (procuring country)

3. Main Findings

The responses of licensing authorities are organized into five sections.

Section 1 AEFI reporting and post-market surveillance

Section 2 Expert advice

Section 3 Human resources and infrastructural capacity

Section 4 Regulatory-industry relationships

Section 5 Expectations among regulators of a Global Vaccine Safety Blueprint

3.1 Section 1: AEFI reporting and post-market surveillance

a) **Low-income countries** rely primarily on passive surveillance of adverse events following immunization; they acknowledge the need for active detection. Low-income countries expect that producing and procuring countries have high quality safety detection systems in place in order to produce and disseminate safety data to procuring countries. This may not be the case; in fact, it appears

that high-income countries do not have a direct role in receiving AEFI reports from procuring countries, seeing this instead as the manufacturer's responsibility. The Brighton Collaboration standard case definitions still remain underused, and countries acknowledge improper knowledge of case definition and causality assessment of AEFI. Fear of accusation, underreporting and lack of knowledge are barriers to reporting in low-income countries.

b) **Middle income countries**. CIOMS reporting forms, as well as Expanded Programme on Immunization (EPI), are used in these countries. Regulators state that the general public can report AEFI in many of these countries. Several issues detract from vaccine safety reporting, including fear by vaccinators and officials concerning the consequences of reporting AEFI. There was wide recognition of the need for improved surveillance mechanisms in these countries.

c) The lack of **high-income country** surveillance for serious AEFI of vaccines exported into low- and middle-income countries represents a major gap in vaccine safety, especially where the major use of these vaccines does not occur in the exporting countries. Regulators report an over-reliance on companies reporting AEFI that needs to be addressed.

3.2 Section 2: Expert advice

a) All **low-income countries** that responded have a national adverse event review committee. Our data show that these countries have concerns with confidentiality and the proprietary nature of information between the expert body that advises the NRA and the national adverse events review committee. Most of these countries appear to be aware of the training and professional background needed to run an effective national adverse event review committee. All countries say they have access to experts, both nationally and internationally. National committee members are based in clinical practice. External experts are called when new vaccines are registered and when national experts are unable to identify or analyse AEFI.

b) With the exception of Belize and South Africa, the **middle-income countries** surveyed all have a national adverse event review committee. National experts are based at universities and in clinical practice. One country indicated having problems with confidentiality between experts. These countries are aware and have good understanding of the professional background, training and expertise required to run an adverse event review committee. International experts are accessible through the Ibero-American Pharmacovigilance Network and WHO. Our data indicate that expert advice is difficult to implement, however, due to infrastructural and institutional factors. External experts are contacted when new vaccines are registered and when deaths occur.

c) **High-income countries** reported having problems with confidentiality between experts. Belgium appears to be the only country that asks its experts to declare their conflict of interest on an annual basis. These countries are aware, and have good understanding of, the type of professional background, training and expertise required to run a national adverse event review committee. Experts are available nationally and internationally, with experts based at universities and in clinical practice. Expert advice is reported to be difficult to implement due to resource limitations. External experts are used on rare occasions and, in some cases, they are called on a case-by-case basis. These countries tend to consult with EMA, FDA, European Centre for Disease Prevention and Control (ECDC) and WHO.

3.3 Section 3: Human resources and infrastructural capacity

a) **Low-income countries** did not express a consistent view as to what would constitute minimal staff requirements (e.g. personnel) for a national vaccine safety system. In terms of infrastructure, these countries state a need for buildings, land, computer equipment and control laboratories. The regulators suggest that the central role of a NRA should involve AEFI surveillance, ensure registration and licensing of vaccines, capture/file AEFI data, and training of personnel.

b) A few **middle-income countries** provided information on what constitutes minimal capacity in terms of staff requirements. In terms of infrastructure, these countries need information and communication technology, and offices and vaccine storage sites. They stressed the central role of communication with manufacturers for NRAs, along with the importance of updating information on safety issues, periodic regulatory inspections and design laws, and policies and protocols to govern immunization.

c) Not all **high-income countries** provided information on what constitutes minimal capacity in terms of staff requirements. Australia explicitly identified a number count (thirteen) for experts needed. Overall, it was stated that the central roles of a NRA involve collecting, monitoring and assessing all safety-related information submitted by the manufacturers, and providing expert advice on weight of evidence of signals detected through the monitoring system.

3.4 Section 4: Regulatory-industry relationships

a) In **low-income countries**, vaccine manufacturers provide information that includes clinical trials data, periodic safety update reports (PSURs), summary of product characteristics and company core data information. The regulators would like additional information, such as AEFI reported in other countries. Meetings with manufacturers are triggered by faulty products, low quality and toxicity issues. Vaccine manufacturers were seen as providing very limited support to low-income countries. These countries often collaborate with manufacturers when the national testing laboratories are unable to conduct special tests. Meetings with manufacturers are requested by the Ministry of Health or the Director General of Health Services.

b) In **middle-income countries**, vaccine manufacturers meet with the NRAs before the submission of intent to file a new vaccine. Cuba is the only country that holds public audiences with manufacturers. Vaccine manufacturers provide safety information to NRAs, which includes clinical trials data, PSURs, risk-management plans for new vaccines and AEFI data reported from other countries. Middle-income country regulators would like additional information that would include, for example, non-clinical studies, quality-attributable aspects and two years of field-safety data (from developing countries) before the product is introduced in the country. Few countries receive support from manufacturers. When support is provided, it assumes the form of training courses. NRAs contact vaccine manufacturers when there is a serious AEFI cluster and repetitive cold-chain complaints. Meetings with the manufacturers are requested by NRAs. These countries indicated that an ideal system to deal with AEFI should be one that is electronic and fast, and that facilitates close cooperation among stakeholders. All middle-income country respondents reported that all manufacturers were willing to work with them.

c) With the exception of France, no high-income country surveyed, explicitly requires vaccine manufacturers to meet the regulator before submission of intent to file a new vaccine application. Rather, manufacturers are "encouraged" to meet regulators prior to filing a new vaccine submission. The safety information provided in meetings with vaccine manufacturers includes AEFI data reported from other countries, clinical trials data, PSURs, summary of product characteristics and toxicology data. Circumstances that prompt meetings with manufacturers include important safety signals, issues in quality control, clinical study plan and new indications. Countries have systems in place for providing and receiving feedback on safety information. Collaborations between regulators and manufacturers assume the form of meetings, roundtables and workshops. Our respondents asserted that, despite some challenges (e.g. unclear AEFI reports), most manufacturers are willing to work and collaborate with them.

3.5 Section 5: Expectations among regulators of a Global Vaccine Safety Blueprint

a) **Low-income countries** expect financial support for the establishment of a national centre for AEFI monitoring, support in transmitting and sharing information on AEFI, reinforcing efforts to control counterfeit vaccines, and short-term consultancy services. These regulators saw the lack of financial resources as a major problem in the creation of a global vaccine safety system. Low-income country regulators asserted that their own national vaccine safety systems could be improved by establishing functional NRAs and national control laboratory (NCL) systems, and training dedicated human resources assigned to deal with AEFI. They considered the key challenges in making these improvements to be political will (commitment) and the lack of clear guidelines (policies).

b) **Middle-income countries** expect rapid exchange of vaccine safety information across countries, assurance that all vaccines are prequalified before licensing for public use, new AEFI guidelines, and technical assistance and capacity building. They saw the main challenges to creating a global vaccine safety system to be in establishing a standardized communication network among countries, political will among governments, and getting stakeholders to be fully involved with the system.

   Regulators of middle-income countries stressed that their own national vaccine safety systems could be improved by having full-time personnel working on AEFI at regional levels, through a global harmonization of an AEFI system and also through stronger commitment from government and the private sector. The challenges in making these improvements are funding, political will, high turnover of personnel, a shortage of qualified professionals and conflicts of interest.

c) **High-income countries** expect transparency in the sharing of vaccine safety information, an early alert system with timely information on safety issues identified within other jurisdictions, and harmonization. Regulators saw the main challenges for the creation of a global vaccine safety system to be gaining agreement on the standards to be applied and funding availability, capacity building in developing countries, compatible reporting systems for database entry, partnerships across public and private organizations, and confidentiality agreements.

High-income country regulators asserted that their own national vaccine safety systems could be improved by moving towards more real-time analysis, use of electronic administrative health data, international collaborations, agreement on a consistent reporting form, and better definition of the communications process. The challenges in making these improvements included resistance to change, and lack of access to administrative electronic data, resources and external communications.

Appendix 1 presents a comparative summary of the knowledge, attitudes, practices and expectations regarding global vaccine safety by regulators from low- middle- and high-income countries.

4. Discussion and conclusions

We identified four main findings from this survey.

4.1 Fear of reporting is an obstacle to AEFI reporting in low- and middle-income countries

In terms of consistent training and education of qualified public-health personnel in low- and middle-income countries, our survey found that there are many challenges to reporting AEFI that relate to fear of accusation, underreporting and lack of knowledge. This was a significant finding of the study that needs special attention. Our respondents stated that political will, as well as resources that target more effective training of public-health officials and vaccinators, could address these issues. These factors have a great impact on both the real and perceived confidence in any vaccine safety system. The lack of understanding surrounding the role of AEFI investigation, notification and communication, as a way to dismiss false information and to increase confidence in vaccinations, is a critical issue. Increased support, including education, training and provision of sufficient infrastructure for local health-care workers, would contribute to alleviating the "fears" (structural misunderstandings about the purpose of reporting) that are reported here. This, however, can only be successful if there is the political will to ensure the expertise, protection and authority of those who report AEFI (i.e. human resources). This issue remains a global challenge.

4.2 Vaccine-exporting countries neither track nor collect AEFI data from low income and procuring countries

The fact that high income, vaccine-exporting countries neither track nor collect AEFI data from low- and middle-income procuring countries might be considered a social justice issue. Furthermore, placing the responsibility for this tracking on the shoulders of the Marketing Authorization Holder might be viewed as a dangerous conflict of interest in regulatory governance. Several countries acknowledged concerns about conflict of interest among their expert advisors. There were some notable differences between high income, and low- and middle-income countries with regard to regulatory acceptance of support from vaccine manufacturers. While high-income countries stated that they received no support from manufacturers, several low- and middle-income countries acknowledged marginal support from vaccine manufacturers, mainly relating to training. Certainly low-income countries recognized a paucity of qualified personnel that affects their capabilities, although even high-income countries expressed a need for more staff, especially as they attempt to move towards more active surveillance.

4.3 Almost all countries indicate that AEFI forms need to be standardized and internationally harmonized

Universally, regulators of countries surveyed wanted to see more fully integrated (harmonized) public-health systems that would also be greatly assisted by the necessary transition from passive to active surveillance of AEFI. Active surveillance remains a critical challenge, even for many high-income countries. Additionally, more work is needed to agree and standardize common documents. Suggestions were made by our respondents for a common AEFI form, for example, that would facilitate consistent reporting within, and across, nations. Currently, both CIOMS and EPI forms are used. There are many different types of reporting forms and systems in place and countries vary in terms of who can access and who can actually report AEFI.

There are a variety of sources of knowledge of adverse events. Regulators reported several different sources of information, including handbooks, but information is scattered across several platforms. To date, no harmonized manual is in use which would guarantee a common understanding of adverse events (e.g. risks and benefits of vaccinations) across sites. A harmonized manual would include, for example, all related documents and forms for notification, information on a standard system for AEFI surveillance, and definitions for adverse events and how to treat them. Regulators stated that manuals should be written in user-friendly language and targeted to a range of specific users (e.g. middle- and upper-level health professionals and fieldworkers). Both low- and middle-income countries voice the need for a stronger commitment from both the government and private sectors for national vaccine safety systems. Our study respondents were united in recognizing that need, and in calling for international harmonization of AEFI safety procedures.

4.4 The key barriers for the development of a global vaccine safety system are resources and the perception of a lack of 'political will' across NRAs

Regulators of most countries, regardless of whether they were high, middle or low income, cited the lack of physical infrastructure and institutional organization as a barrier to sufficient and effective AEFI surveillance. Furthermore, lack of electronic records (e.g. well documented databases) and quick access to AEFI reports from other countries is experienced, particularly in low- and some middle-income countries. They see the main challenges to the creation of a global vaccine safety system to be a standardized communication network among countries, political will among governments, and fully engaged stakeholders. Regulators of all countries were united in calling for international harmonization of AEFI safety data collection, reporting, and information exchange. They identified the need for strengthening the NRA functions and pharmacovigilance centres in all countries. This network would be integral to data exchange in a global vaccine safety system. Functional regulatory authorities remain a challenge for low-income countries that lack the financial and human resources to build the capacities and capabilities necessary for regulatory harmonization.

5. Limitations

The regulatory survey was sent to a designated regulatory official in the selected countries. Our results were dependent on the knowledge and information from those officials. Some countries chose to have one individual respond. Other countries had two or three different officials working on different sections of the survey, in accordance with their particular expertise. Intra-rater reliability was not assessed, nor was inter-rater reliability; those surveys that were completed by a single respondent may represent that respondent's particular knowledge. We were not able to corroborate or verify their responses.

Appendix: Global vaccine safety matrix

	AEFI reporting and post-market surveillance	Expert advice	Human resources and infrastructural capacity	Regulator-industry relationships	Expectations of a global vaccine safety blueprint
LOW INCOME COUNTRIES	• AEFI are identified through a voluntary system • AEFI guidelines are not readily accessible for queries • AEFI are reported by paper • National and EPI forms are used to report AEFI • AEFI are reported by health-care personnel (medical doctors, nurses, midwives and vaccinators) • Health-care institutions operated by national governments are responsible for AEFI reporting and collecting • Challenges to reporting AEFI: fear of accusation; underreporting and lack of knowledge • Gaps in vaccine safety systems: NRA is not directly involved with the present AEFI monitoring system; inadequate knowledge of various AEFI • Critical elements necessary for reliable reporting and surveillance of serious AEFI: clear case definitions; immunization history; laboratory and investigation reports • Physical resources needed: local AEFI forms; computers for data entry and internet access; computers; suitable database and trained staff • AEFI barriers: paper forms have to be scanned and sent by email; problems of notification caused by low internet speed; lack of national committee for AEFI causality assessment	• All countries have national adverse event review committees • Confidentially issues among experts • All countries have access to experts nationally and internationally • National adverse events review committee members are based in clinical practice and academia • Countries able to implement suggestions of a national adverse events review committee • External experts are called when national experts are unable to identify, detect or analyse AEFI and when vaccines are not WHO prequalified • NRAs consult with other countries when there are quality or safety concerns about the vaccines	• Infrastructural resources needed: land; buildings; utility services; national control laboratory; computerized systems; qualified personnel • Suggested role for NRAs: 1) NRA has the sole responsibility for ensuring registration and licensing of any vaccines to be imported or manufactured locally by law; 2) collect data and train health-care personnel	• Vaccine manufactures meet with health regulators before submission of intent to file a new vaccine • Meetings with vaccine manufacturers are triggered by faulty product/low quality • Meetings with vaccine manufacturers are perceived to be useful • Vaccine manufacturers provide limited support to low-income countries • NRAs collaborate with industry when the government testing laboratory is unable to conduct a special test and there are activities in connection with the development of the AEFI surveillance system • Collaboration with industry assumes the form of training (e.g. workshops) • Meeting with vaccine manufacturers is requested by health-care authorities (e.g. Ministry of Health or NRA if there is one)	• Expectations from a global vaccine safety system include: provide sources of information; update links to other more stringent regulators for information; reinforcing efforts to control counterfeit vaccines • Challenges for the creation of a global vaccine safety system include: improving collaboration over vaccine licensing; financially weak countries need to be supported by the richer countries by providing free technical know-how for production and quality control of vaccines • National vaccine safety systems can be improved by establishing functional NRAs; trained human resources assigned to dealing with AEFI. Challenges in making improvements include: political commitment; clear guidelines and action plan implementation

	AEFI reporting and post-market surveillance	Expert advice	Human resources and infrastructural capacity	Regulator-industry relationships	Expectations of a global vaccine safety blueprint
MIDDLE INCOME COUNTRIES	• Most countries identify AEFI through passive surveillance systems • All countries have national guidelines for AEFI surveillance • AEFI surveillance guidelines are available in electronic form for most countries • Most countries say they have a single national structured and pre-coded AEFI report form (designed by EPI or CIOMS) • Institutions responsible for AEFI reporting and data collection include: Ministry of Health (Belize), Nation Committee of AEFI (Indonesia), National Pharmaceutical Control Bureau (Malaysia), National Adverse Drug Reporting Centre (South Africa), and Bureau of Epidemiology (Thailand) • Challenges in reporting AEFI include: underreporting of minor reactions; lack of qualified personnel; timeliness and late reporting • The main barrier that undermines AEFI surveillance systems is "fear of reporting"	• Most countries have national adverse event review committees • Very few countries have confidentiality issues among experts • Expertise required to operate a national adverse review committee is available nationally • Experts available nationally are based in universities and in clinical practice • Expert advice is difficult to implement due to infrastructural and institutional factors • External experts are called when death occurs, every time a new vaccine is registered • NRAs consult with other countries when there are problems with vaccines and when critical decisions on national immunization needs need to be designed and implemented	• Experts available nationally • Very few countries determined and defined "minimal capacity" in terms of personnel • Lack of motivated qualified professionals • Infrastructural and capacity resources needed: trained personnel; better information and communication technology; construction of a national vaccine store designed for stock intake and issuance; appropriate cold boxes for transportation • Suggested role for NRAs: safety evaluation; risk management; risk mitigation; AEFI monitoring signal detection; monitoring and surveillance of vaccine manufacturers	• Vaccine manufacturers meet with the NRA before the submission of intent to file a new vaccine • Meetings are requested with vaccine manufacturers if there are violations of GMP that results in unreliable quality vaccine • Collaboration with industry assumes the form of training (e.g. conferences and workshops) • NRAs collaborate with industry when new guidelines are being developed; discussion and clarification of complaints relating to specific products and when AEFI cases need to be investigated further • Meetings with vaccine manufacturers are requested by NRAs • Communication with vaccine manufacturers takes place through official letters, email, fax and teleconferencing • When conflicts of interest arise, these are sent to ethics committees and transparency is requested by NRAs	• Expectations from a global vaccine safety system include: to facilitate fast exchange of vaccine safety information across countries; assurance that all vaccines are prequalified before licensing for public usage; to provide assistance and guidance • Challenges for the creation of a global vaccine safety system include: political will among governments; getting stakeholders to be fully involved with the system; lack of qualified/ skilled personnel • National vaccine safety systems can be improved by: forming a well-structured regulatory body; effective monitoring distribution system; continuity of professionals; well-equipped health-care facilities; through a global harmonization of an AEFI system. Challenges in making improvements include: political will; conflict of interest; limited funding

	AEFI reporting and post-market surveillance	Expert advice	Human resources and infrastructural capacity	Regulator-industry relationships	Expectations of a global vaccine safety blueprint
HIGH INCOME COUNTRIES	• AEFI forms can be submitted by anyone • High-income countries do not receive nor collect AEFI data directly from procuring or low-income countries • The Marketing Authorization Holder is required to collect AEFI data from procuring countries and prepare periodic safety update reports (PSURs) • AEFI from procuring countries are reported via the manufacturer only • Most countries do not track the AEFI of vaccines once they have been exported • AEFI cases are identified via passive surveillance through public- health authorities • High-income countries do not provide assistance to procuring and low-income countries • AEFI guidelines are available online • AEFI reports are submitted by paper, internet, websites, telephone and fax • Most countries have more than one AEFI form • Most countries face challenges associated with passive surveillance/reporting systems • Key gaps in AEFI surveillance/ reporting systems: limited immunization registry systems and electronic medical records; lack of a consistent nationally agreed reporting form	• With the exception of Estonia, these countries have national adverse events review committees (also known as advisory committees) • National adverse events review committee members are based in academia, clinical practice and government • Expert advice is difficult to implement due to resource limitations • Experts are from academia, clinical practice and regulatory sectors • External experts are rarely used • External experts are called when causality is doubtful, difficult to relate to the product and when the consequences of the decision have policy and/or guidance implications • NRAs consult with other countries in order to discuss safety signals and global public-health concerns.	• Expertise is available nationally • Infrastructural resources needed: memorandums of understanding with public- health agencies; reliable databases and signal analysis and statistical skills • Suggested role for NRAs: collecting; monitoring and assessing all safety-related information submitted by the manufacturers; making safety information available; provide expert advice on weight of evidence of signals detected through the monitoring system	• With the exception of France, no high-income country has explicitly stated that vaccine manufacturers meet the regulator before submission of intent to file a new vaccine application • Additional vaccine safety information is requested on a case-by-case basis • Meetings with vaccine manufacturers when there are issues in quality control that might have an impact on the safety and/or efficacy/effectiveness of the vaccine and whenever the cost/benefit ratio of a vaccine is in question for reasons of safety • Meetings with manufacturers are reported to be very useful • Countries have systems for providing and receiving feedback on safety information • NRAs do not receive support from vaccine manufacturers • Collaboration with vaccine manufacturers assumes the form of a roundtable to discuss ongoing regulatory issues of interest to the industry • NRAs expect manufacturers to respond timely and rapidly • Most countries have guidelines to deal with conflict of interest	• Expectations from a global vaccine safety system include: easy, transparent sharing of vaccine safety information; early alert system; timely information on safety-issues identified; harmonization • Challenges for the creation of a global vaccine safety system include: agreement on the standards to be applied and funding availability; capacity building in developing countries; memorandum of understanding for sharing confidential information; compatible reporting systems for entry into database, and ensuring that vaccines reach the populations intended with the information necessary to ensure their safety • National vaccine safety system can be improved by: data linkage; nationally consistent reporting form and processes; implementation of an active surveillance system; more networking and better definition of communications process • Challenges in making improvements include resistance to change, and lack of access to administrative electronic data

	AEFI reporting and post-market surveillance	Expert advice	Human resources and infrastructural capacity	Regulator-industry relationships	Expectations of a global vaccine safety blueprint
HIGH INCOME COUNTRIES	• Physical resources necessary for AEFI: IT support; clear guidelines; regional and national collection centres; notification forms • Barriers for implementing AEFI reporting standards: training; voluntary reporting; lack of standardized AEFI • Needs for a reliable AEFI reporting include: agreed reporting format; multiple streamlined ways to report; active surveillance of specific AEFI, and more awareness among health professionals				

Survey of vaccine manufacturers

Executive summary

As part of the WHO vaccine safety blueprint project, between mid-June and mid-July 2010, ii4sm conducted a survey of vaccine manufacturers, both multinational and from developing countries. The survey gathered important information about vaccine post-marketing surveillance systems, the flow of information between companies and regulatory authorities, and the expectations for a global vaccine safety partnership within developing countries. This document describes the results of the survey, with descriptive analyses. It was not the purpose of the survey to perform a quantitative analysis, hence such questions as, numbers of vaccines sold or number the AEFIs received from low- and middle-income countries, were not included in the questionnaire.

1. Introduction

This describes and summarizes the results of the WHO survey of vaccine manufacturers, to characterize the value and limitation of vaccine safety data available through their system, and to gather their perspective on the need for a global vaccine safety system, including their possible role in such a system. This baseline survey addressed the following elements:

- a description of the vaccine post-marketing surveillance systems available to large manufacturers of vaccines for global programmes;
- an analysis of the flow of information between the manufacturers and regulatory authorities in producing and procuring countries;
- a survey of manufacturers' expectations for a global vaccine safety partnership, including an analysis of possible models of collaboration between the public sector and industry.

The survey addressed the 12 largest vaccine manufacturers — six multinational companies and six companies from developing countries. The survey was a web-based questionnaire divided into three separate topics, and was conducted between mid-June and mid-July 2010. The major outcomes of the survey are presented in the results section. The Appendix contains the survey questions with summarized and graphically displayed responses.

2. Results

Of the 12 vaccine manufacturers (six multinational companies and six companies from emerging markets), 11 participated in the survey. One multinational company did not respond.

2.1 Overview

The survey was set up to obtain a description of vaccine post-marketing surveillance systems and potential issues applicable to large manufacturers of vaccines for global programmes. In addition, the survey seeks to analyse the flow of information between the manufacturers and regulatory authorities, and the manufacturers' expectations for a global vaccine safety partnership, including possible models of cooperation between public and private sectors. The web-based survey was addressed to 12 large vaccine manufacturers, six multinational and six from developing countries. However, one multinational company did not participate in the survey (without specifying the reasons), giving a slight imbalance in favour of the vaccine manufacturers from developing countries. Overall, the results are in line with expectations, and showed that vaccine manufacturers are interested in improved safety data from low- and middle-income countries. It might be worthwhile to develop a more detailed questionnaire, based on the responses shown in this survey, to facilitate a quantitative evaluation.

2.1.1 Summary Topic 1

Post-marketing surveillance system and flow of information between the manufacturer and regulatory authorities

All vaccine manufacturers have post-marketing surveillance systems in place for capturing AEFIs. These systems are paper-based or electronic systems, either from a commercial source or the company's own in-house system. The regional distribution of actual captured spontaneous adverse events for a vaccine per year, is heterogeneous, depending on the size and market penetration of the company; spontaneous reporting from north and southern Africa, for instance, is particularly sparse. The sources of information that input into the pharmacovigilance system is either through government immunization programmes or through commercial distribution. The majority of companies use both sources of information. Only one company from emerging markets uses a non-governmental, non-commercial source of information, and this is a vaccine safety advisory committee.

All vaccine manufacturers have procedures for case management and plans for urgent notification in place (e.g. change in labelling, healthcare professional letter), or implementations of restriction of use due to newly perceived risks, as evidenced from their process details provided. The companies have different ways of dealing with the eventuality that a report associates a vaccine with three deaths. Their responses depended on whether the vaccine is directly marketed in a country by the company itself, or is distributed through an official programme (EPI) of a non-governmental organization (NGO). In the first instance, a designated contact person would be responsible for collecting and communicating the data, with some of companies having a centralized procedure in place to share the data in expedited fashion with the national-health authorities, ethical committees and relevant company departments. In the second instance, where the vaccine is distributed through an EPI, the case data would be

communicated by the official organization. There seems to be room for improvement regarding the timeliness and formal way of communication from the NGO to the vaccine manufacturer. However, it was pointed out that the role of the WHO is critical in reporting AEFIs in these countries to manufacturers.

Companies are almost equally divided on the question of whether there are differences or not between countries regarding the reporting and investigating of adverse events. However, twice as many companies from emerging markets than multinational companies find differences between countries. Multinational companies could have more centralized processes installed than companies from emerging markets that could alleviate some of the perceived country-by-country variations. Plus, if a company perceives reporting and investigating of AEFIs as equally good or poor in several countries, then the company would not report variations between countries. Therefore, the proportion of responding may reflect the rationale as to how the respondent made the baseline assumption.

A greater role for the WHO would be welcomed to intervene in countries where there is perceived unwillingness of the national health authorities to cooperate.

Companies are also divided on the question of whether the pharmacovigilance regulations in low- and middle-income countries are being used, are clear and up-to-date. This seems to be mostly dependent on the development status of the country, with developed countries like Brazil, China and India, Malaysia and Thailand being named as having clear and up-to-date pharmacovigilance regulations in place. Surprisingly, Bangladesh is also mentioned, but here the reporting is through the WHO. All in all, the results should be interpreted with caution, as some companies had only experience with pharmacovigilance regulations in their home country and, hence, knew the local conditions best. Interestingly, India is cited as an example where spontaneous reporting of adverse events is rather rare. In addition, some multinational companies state that, in the majority of low- and middle-income countries, no pharmacovigilance regulations exist. There is an enormous need to improve, keep up-to-date and even to establish pharmacovigilance regulations in most of the low-and middle-income countries. This could be facilitated through the WHO as an independent and recognized authority.

As expected, all vaccine manufacturers declare to ensure patient confidentiality. Most of the companies have risk minimization plans based on pharmacovigilance data installed either globally, or dependent on the country or product.

The majority of the vaccine manufacturers have access to an external database that could be used for capturing AEFIs; however these sources are employed for validating or testing safety signals. In low- and middle-income countries, there does not seem to be access to such databases available.

The majority of companies do not have a checklist of roles and responsibilities available from a previous or ongoing vaccine safety surveillance system in a developing country. However, it might be that the companies are only referring to their relationship to NGOs, as it is most unlikely that multinational companies do not have lists in place of roles and responsibilities for contacts and activities. This lack of clear definition of roles and responsibilities among manufacturers, NRAs and NGOs, or other organizations, underscores the global, regional and country level needs of coordinating pharmacovigilance effort among the stakeholders involved.

2.1.2 Summary Topic 2

Based on experience in developed countries that could be adapted for developing countries

Although most vaccine manufacturers think that a global harmonization of AEFI forms can be achieved, it is more important for them to standardize common fields and agree on a minimum level of completeness acceptable to all stakeholders. Areas difficult to harmonize are: data collection; reported event terms; definition of AEFI; medical review and management; causality assessment; standard of care; terminology; patient's vaccination history; vaccine source, and regional levels in the quality of reporting that would need a strong involvement by WHO and other stakeholders for harmonization. These areas could be used as a basis for developing a strategy for harmonization of vaccine-safety issues.

Interestingly, the vaccine adverse event form that was developed by the Brighton Collaboration is rarely used by companies and, if used, it is rather for data categorizing and analysis than for data collection. Therefore, it seems that any harmonization effort of datafields could not use an existing set of datafields, but would require discussion with all relevant stakeholders to come to an agreement. The question of granting legal authority to companies for an autonomous AEFI investigation gave a mixed result, suggesting that the implication of the question, at least in part, was not well understood; hence it is hard to draw any meaningful conclusion from it. By contrast, there was complete agreement that the manufacturer should participate in the investigation of an AEFI related to its product.

The use of different communication channels largely depends on audience and country, with most manufacturers using two or more channels to communicate with health authorities and the general public. Most companies like the idea of having an international publication with information and educational material on AEFI, although it was cautioned that it should be used only for the most important safety concerns that would be relevant for the public, and suggesting that a respected organization (e.g. WHO) should be responsible for publishing such a journal.

The ranking of improvements needed by the companies reveals the four priority areas in descending order: active surveillance; passive surveillance; access to global safety data, and health database analyses.

Although there are positive opinions, some companies are pessimistic that passive surveillance systems would work in developing countries, indicating that active surveillance is the preferred way to monitor adverse events in these countries. However, this would require substantial resources to build the necessary infrastructure, and this might be unrealistic to achieve. On the other hand, an intensified and well-planned enhanced surveillance in selected settings might be a very useful tool in developing-country settings to detect signal or collect AEFI data.

Surprisingly, companies have divergent views on (interventional) clinical studies, ranging from most useful to limited value. Observational studies are also seen as useful, but highly dependent on regional resources. Immunization registry and health database analyses are generally considered valuable, but generally unavailable in developing countries, and would need to be linked to each other. In addition, the importance is stressed of linking the vaccination report with the associated AEFI to perform a meaningful analysis. Access to global safety data is generally seen as helpful, but only if the quality of data would be assured, and consolidated information would be reviewed by a qualified group, or under the auspices of a reputable institution.

All vaccine manufacturers agree that education of health-care professionals in developing countries is important to improve, for example, the quality of AEFI reporting.

In general, companies have strong negative opinions about the use of local media tracking, thinking that it has no use in pharmacovigilance because it would exaggerate individual AEFIs and not give the whole picture. The companies have divided opinions on political recognition, with some companies finding it essential to improve vaccination programmes, whereas others find it useless. In general, vaccine-safety issues seem to be very political in low- and middle-income countries where populist measures may be undertaken in the case of safety issues without proper investigation. However, it might be difficult to maintain sustainable political recognition of vaccine issues (including safety), given that key positions within governments tend to change frequently.

2.1.3 Summary Topic 3

Manufacturers' expectations for a global vaccine safety partnership, including an analysis of possible models of collaboration between the public sector and industry

Although most companies report partnerships with governments and NGOs outside of national pharmacovigilance programmes, fewer of them report issues within these partnerships. Recommendations to address issues are focused on the conditions in which the companies would be willing to enter into a partnership, such as the prior establishment in writing of clear responsibilities and obligations of the partners, and a prior agreement on how to interpret safety data.

Within a partnership, industry would largely provide resources in the areas where their strengths lie, for instance, financial support or technical expertise (e.g. in data collection, analysis and interpretation). In addition, companies would assume responsibilities in the areas of safety monitoring, data collection and analysis, and AEFI-reporting and investigation.

A harmonized AEFI coding dictionary, that could be used for reporting in developing countries, is strongly favoured by companies from developing countries. Multinational vaccine manufacturers are cautious in this respect, in that AEFI terms need to be based on the Medical Dictionary for Regulatory Activities (MedDRA), and Brighton Collaboration terms, to be useful.

In general, data sharing with other companies seems to be a sensitive issue, and is restricted to high-level information or to marketing partners.

Most companies, but not all, favour a strong degree of cooperation with national immunization programmes, the National Regulatory Authority and manufacturers, regarding detection, investigation and reporting of AEFIs. A similar picture emerged from the questions regarding the degree of cooperation between the manufacturer and the public-delivery service of the country using the vaccine. Here again, companies show a tendency to favour both strong and medium cooperation. However, regarding the investigation of AEFIs, one multinational company wants no cooperation at all.

Companies are also of the opinion that the degree of cooperation between countries that produce vaccines, and the countries into which it is exported, should be strong.

There is universal agreement that there should be a strong degree of common awareness between company headquarters and national affiliates regarding detection, investigation and reporting of AEFIs.

Companies favour different options (e.g. web platform, newsletter, or email) regarding the sharing of AEFI data between the company and NGOs.

The companies had many suggestions regarding the minimum capacity requirements in the areas of infrastructure, workflow and information flow, reflecting the need for establishing a system necessary for adequate AEFI monitoring in developing countries. To summarize, there are similar minimum capacity requirements for all three areas including: qualified staff; standardized trainings, secure communication infrastructure, and the establishment of a passive surveillance system. However, the availability of qualified staff seems to have high importance, which implies a major effort, either by the manufacturers or WHO, to train them. Manufacturers' responses to the minimum capacity questions illustrated that the area of needs perceived by manufacturers are not very different from those of WHO: personnel training; IT and communication; surveillance system strengthening, and the establishment of a reliable database in the country. The establishment of regional sentinel sites and/or country-level immunization centres for monitoring and coordinating of AEFI and pharmacovigilance-related activities might be an important step for the improvement of vaccine safety.

There are many diverse suggestions for pharmacovigilance process improvement and pharmacovigilance partnership outcome. A further questionnaire, giving the option to prioritize the suggestions according to their importance, could indicate where the most pressing requirements are.

Baseline assessment of the vaccine safety systems in the WHO global post-marketing surveillance network countries

Executive summary

As part of the Global Vaccine Safety Blueprint project, in 2010 a baseline assessment of the vaccine safety systems was carried out in 11 countries which are part of the WHO Global Network for Post-marketing Surveillance of Prequalified Vaccines. The primary objective of this baseline assessment was to contribute to a landscape analysis of vaccine safety systems in low- and middle- income countries. The landscape analysis, in turn, will be used to define elements of minimal capacity for establishing vaccine safety systems in developing countries.

The baseline assessment was carried out via email using a questionnaire that was self-completed by representatives from the 11 network countries, plus telephone interviews with those representatives to clarify and validate the data collected. Data were collected in six areas: (1) structure and management of AEFI system; (2) AEFI surveillance functions [reporting and data management, case investigation and analysis]; (3) national immunization safety committee; (4) communication with concerned groups; (5) information, education and communication; (6) vaccine utilization.

The key findings of the baseline assessment are presented in this report.

1. Introduction

In 2009 in selected countries, WHO launched the Global Network for Post-marketing Surveillance of Prequalified Vaccines (hereinafter referred to as "the PMS Network"), to improve post-licensure vaccine safety data and to help deal with challenges relating to access to reliable safety data, particularly in the context of investigation and management of serious AEFIs. The main objective of the PMS Network is to develop a standardized approach for monitoring and assessing serious, rare or unexpected AEFIs with newly prequalified vaccines. To achieve this, the PMS Network aims to strengthen the existing AEFI surveillance system in member countries. As part of PMS Network activities, a country profile (CP) tool was developed, in order to collect basic information relevant to AEFI surveillance systems, such as core elements of immunization programme capacity and activities for AEFI surveillance, regulatory capacity in general, and availability of health indicators relevant to assessment of vaccine safety. The primary purpose of the CP tool was to gather baseline information on selected variables relevant to the Network in order to facilitate comparisons among the PMS Network countries with respect to their vaccine safety data. The baseline CP data would also help identify areas that require country-specific technical support in an effort to harmonize, where possible, the AEFI surveillance tools and methodologies used in the Network countries.

In February 2010, WHO initiated the Global Vaccine Safety (GVS) Blueprint project, which includes a set of studies (Activities 1.1–1.7) to provide a landscape analysis of the existing vaccine safety systems in low- and middle-income countries. The landscape analysis, in turn, will be used to define elements of minimal capacity for establishing vaccine safety systems in developing countries. Within the framework of this initiative, a baseline assessment of the vaccine safety systems in the WHO Global PMS Network countries (also known as Activity 1.5) was conducted between May and November of 2010. This baseline assessment was carried out as an extension of the previous country profile assessment. The activity was implemented by a WHO consultant in close collaboration with the WHO blueprint project secretariat, and experts from the blueprint project collaborative group. The technical oversight committee of the PMS Network provided additional inputs in order to ensure a consistency of approach with the methods used previously.

2. Objectives

The primary objectives of Activity 1.5 were to carry out the baseline assessment of the vaccine safety systems among 11 PMS Network countries, and to provide an analysis and report to be incorporated in the overall landscape analysis of vaccine safety in low- and middle-income countries, for development of the global vaccine safety blueprint.

Activity 1.5 also had, as secondary objectives, to provide complementary data to Activities 1.3 (survey of vaccine regulators), 1.6 (analysis of NRA assessments) and 1.7 (financial analysis), within the framework of the blueprint project.

3. Methodology and analysis

The following 11 PMS Network countries participated in this baseline assessment of AEFI surveillance systems: Albania, Brazil, India (Maharashtra State), Iran (Islamic Republic of), Kazakhstan, Mexico, Senegal, Sri Lanka, Tunisia, Uganda, and Viet Nam. For confidentiality reasons, we substituted the names of the countries by numbers from 1 to 11.

The baseline assessment was carried out via email using a standard questionnaire which was self-completed by representatives from the 11 PMS Network countries, followed by telephone interviews with representatives of those countries for discussion, clarification and validation of the data collected.

The questionnaire for the baseline assessment was developed in consultation with the WHO Secretariat, the GVS blueprint collaborative group and the technical oversight committee of the PMS Network, and was reviewed by WHO regional offices and the consultative committee of the GVS blueprint project.

The questionnaire was built on the previously developed CP tool, in order to provide additional information to complement data previously collected during the CP survey in PMS Network countries. The main strategy of the current baseline assessment was to review, refine and analyse the vaccine safety system components in those countries, and to document the infrastructure, systems and tools that could be considered to define the notion of minimal capacity to ensure vaccine safety in PMS Network countries.

The final (i.e. administered) questionnaire was comprised of groups of questions focused on the following:

1) AEFI system
   – structure and management of the AEFI system;
2) AEFI surveillance functions
   – reporting and data management;
   – case investigation and analysis;
3) national immunization safety committee
   – structure, activities and management of serious AEFIs;
4) communication with concerned groups
   – information, education and communication;
5) finance[1]
   – quantification of the human and infrastructural resources for financial analysis;
6) vaccine utilization.

At least two focal points responsible for AEFI surveillance (from EPI, NRA or the National Pharmacovigilance Centre, and a WHO staff member as liaison in one case) from each PMS Network country were identified at the beginning of the survey on the basis of their active participation in the PMS Network project. All the data collection was performed with the collaboration of representatives of the WHO regional offices.

The AEFI focal points were contacted via email and requested to complete the questionnaire and validate previously collected information relevant to the AEFI surveillance system in their countries. Usually, one of two country representatives was contacted subsequently to provide a detailed telephone interview conducted by the consultant.

The AEFI focal points from the following institutions participated in the interview:

1) EPI staff from 8/11 PMS Network countries;
2) NRA staff from 1/11 countries;
3) EPI and NRA staff from 1/11 countries.
4) In 1/11 countries, due to language difficulties, the telephone interview was conducted with staff from the WHO Regional Office for the Americas and the WHO country office. WHO staff from the regional office and the country office had also facilitated completion of the questionnaire.

[1] The information collected in section V. Finance was submitted to the financial analysis team responsible for Activity 1.7 of the blueprint project for review, analysis and interpretation of the financial aspect of AEFI systems in the PMS Network countries.

The baseline assessment questionnaire included, primarily, multiple-choice questions and close-ended questions, while a small number of questions were open-ended questions.

In 10 out of 11 PMS Network countries the multiple-choice questions about different activities and functions were focused mainly on three administrative levels; the national, sub-national and health-facility levels. The three levels were defined as follows in the assessment:

- national level – the Ministry of Health or any institution at the country level;
- sub-national level – institutions at intermediate level, such as regional or other equivalent, where information is collected from districts and municipalities to be submitted to the national level;
- health-facility level – the most peripheral level in the health system e.g. immunization centre, district or municipal hospitals, etc.

The data collected from Activity 1.5 were then entered into a Microsoft Excel® file for subsequent analysis. The results of the survey are primarily based on descriptive analyses.

4. Summary of the key findings

4.1 Structure and management of AEFI system

All 11 countries have AEFI surveillance systems in place involving three or four administrative levels in the AEFI reporting flow. The national EPI is responsible for AEFI reporting in all PMS Network countries (Table 1). In 5/11 countries both the EPI and NRA are in charge of vaccine safety concerns in the country. In four of them, it is a collaborative endeavour between the EPI and NRA, since both organizations are actively involved in AEFI surveillance activities (Table 2).

There are slight differences in collecting AEFI reports from the public and private sectors in some countries. Six of 11 countries stated that they receive reports from the private sector. In four out of six reported PMS Network countries, both EPI and NRA are responsible for the AEFI reporting system. In two of them, EPI is responsible for collecting AEFI reports from the public sector and NRA coordinates AEFI reporting with the private sector.

Overall, the EPI and NRA collaborate regularly, although, in some countries, there is a limited collaboration between these institutions, due to unclear roles and responsibilities in the AEFI surveillance system and also ways of mutual sharing and storing of AEFI data. All countries have a National Pharmacovigilance Centre.

The data from the previous country profile survey and this baseline assessment of AEFI systems in the PMS Network countries showed the existence of at least two designated national focal persons responsible for AEFI surveillance. In all countries, one of the two focal points is a representative of the EPI while the second focal point is a representative of either the NRA or the National Pharmacovigilance Centre.

In all PMS Network countries, the AEFI surveillance system is covered by law or other regulations, and usually supported by national AEFI surveillance guidelines. The guidelines are distributed among staff involved in AEFI surveillance at all levels in 10 countries, and in 1/11 countries, at the national and sub-national levels only. Nine PMS Network countries have documented the roles and responsibilities of key players involved in AEFI surveillance, and these are usually described in the national AEFI surveillance guidelines (Table 1).

A generic flow chart for AEFI reporting is shown in Figure 1 based on flow charts provided by the 11 PMS Network countries. The blue boxes with * in this generic flow chart are common elements for all PMS Network countries.

In general, the following health professionals are involved in AEFI surveillance.

Health-care workers (physicians, nurses, other health-care workers) – responsible for detection, reporting and management of AEFI in six countries.

Health supervisors at sub-national level (district and/or regional epidemiologist) – responsible for monitoring of AEFI reporting and assistance in AEFI case investigation.

In serious AEFI cases, a hospital staff usually notifies the focal point for AEFI surveillance at the sub-national level. In some countries, this focal point, together with the local investigation team, will finalize the AEFI reporting form and will be in charge of AEFI investigation. The information will be simultaneously submitted to the EPI and/or NRA or National Pharmacovigilance Centre at the national level. In a few countries, the sub-national level is the "relay point" and during a crisis situation the staff from health- facility level report directly to the national level which is in charge of case investigations.

National focal point – responsible for coordinating the identification and reporting, and investigating the AEFI in their respective states, regions or oblasts, plus assistance and communication with media, and reviewing overall pattern of reports and investigation.

Usually the national focal point(s) for AEFI surveillance participates in the case investigation.

Database team (including person for data entry and data manager) – is responsible for maintenance of the national database of AEFI cases.

EPI – systematically monitors the occurrence and investigation of all AEFI cases, especially severe or serious cases, and is also in charge of monitoring vaccine distribution and administration (records of lot/batch number, if any) and communicates with NRA.

NRA and/or pharmacovigilance centre – is in charge of regulatory issues. In some countries, additional roles of the NRA were reported as post-marketing surveillance, and data mining and reporting to the Uppsala Monitoring Centre. These institutions also collaborate with the EPI regarding the reported AEFI data in order to identify safety signals that merit intervention. In some countries, they are responsible for AEFI surveillance and collaboration with the private sector. Four of 11 PMS Network countries have active collaborations between two institutions. In 1/11 PMS Network countries, the implementation of the AEFI surveillance system involves additional institutions such as universities, with links maintained with the NRA and EPI. Some representatives of PMS Network countries suggested redefining and clarifying the roles of the two parties (EPI and NRA) regarding AEFI surveillance.

Immunization safety committee or expert committee for causality assessment of AEFI – are responsible for review of AEFI case investigation and final classification of severe and serious AEFI cases. The committee is usually represented by immunologists, paediatricians, forensic pathologists, infectious disease and neurology specialists, and epidemiologists, and members from EPI and NRA.

Private sector – the data provided indicated that the private sector is not involved in AEFI surveillance system activities in five PMS Network countries. Accordingly, AEFI notifications are received from the private sector only in the remaining six PMS Network countries.

4.2 AEFI surveillance functions

4.2.1 AEFI reporting tools

All PMS Network countries have national AEFI reporting forms. In 1/11 PMS Network countries the same standardized form is used for reporting to both the EPI and NRA; this can be considered as a best practice by other countries (including PMS Network countries, where applicable).

There is a substantial variation in the list of reportable AEFIs in the countries surveyed. All 11 countries have guidelines specifying reportable adverse events. Six out of 11 countries specify reportable events that are consistent with the WHO generic guidelines "Immunization safety surveillance: guidelines for managers of immunization programmes on reporting and investigating AEFIs" [WPRO/EPI/99.01]. According to the content of the list of reportable AEFIs, the PMS Network countries can be divided into four groups.

1) First group of countries, whose list of reportable AEFIs is described as list of local and rare vaccine reactions, e.g. anaphylactoid, anaphylaxis, hypotonic-hyporesponsive episode (HHE), toxic shock syndrome (TSS), severe local reaction, sepsis, etc.

2) Second group of countries, which has more general recommendations to report, like any death, hospitalizations, clusters, suspected vaccines, or other severe and unusual events that are thought by health workers or the community to be related to immunization, and a list of vaccine reactions.

3) Third group of countries, which has a list of reportable AEFIs with all the recommendations mentioned above.

4) In the last group of countries, the information is either not available or not clear.

Ten PMS Network countries distribute the list of reportable AEFI at all levels. In 1/11 PMS Network countries, the list of reportable AEFI is not available among staff at the health-facility level, but is distributed among AEFI focal points.

Similarly, only 5/11 countries use AEFI case definitions recommended by WHO, and in only 1/11 countries the NRA reported use of the Brighton Collaboration case definitions for reporting. The rest of the countries stated different sources of AEFI case definitions used. In 8/11 PMS Network countries the current case definitions are circulated at all levels, while the remaining 3/11 countries reported that the definitions are only distributed at the national level.

Although nine PMS Network countries declared availability of written procedures for actions to be taken (e.g. reporting and case management), in the case of serious AEFIs or clusters (Figure 2), only one country provided such documents for review and validation.

The officially recommended timeframe for reporting of serious AEFI in 10 countries is 24–48 hours, with the exception of one which does not have a specific timeframe (Figure 3). All PMS Network countries stated that "usually" all serious adverse events and death cases are reported immediately, or within 24–48 hours after occurrence, by all means of communication.

The timeframe of reporting for non-serious AEFI cases is specified in the majority of PMS Network countries, and non-serious AEFIs are usually reported on a monthly or weekly basis (Figure 4). Reporting in nine countries is mandatory for serious AEFIs at all levels, and in five countries for non-serious AEFIs, also at all levels (Figures 5, 6). However, the reporting of AEFI is voluntary in two PMS Network countries.

Even in those countries with mandatory reporting, underreporting of AEFI cases is observed. Fear of punishment and a limited appreciation by health-care workers of the significance of AEFI reporting, were noted as some possible explanations of underreporting.

All 11 PMS Network countries are using case-based data reporting tools at the health-facility level (Figure 7). In addition to case-based data, eight countries use a line-listing format to report AEFI data and seven countries use aggregated data.

The data provided indicates that the private sector is not involved in AEFI surveillance system activities in five PMS Network countries. Only in six countries are AEFI notifications collected from the private sector.

4.2.2 Data management

In 10 PMS Network countries, the AEFI data coding/entry is performed at the national level. In three countries, the data coding/entry is performed at both the national and sub-national levels. There is at least one database manager at the national level in nine PMS Network countries.

4.2.3 Case investigation and analysis

In this section, it is important to note that the baseline assessment questionnaire did not define or specify the level of AEFI case investigation.

Written procedures for case investigation are available at the national level in eight PMS Network countries and at all levels in six of them (Figure 8). Case-investigation forms are available in all PMS Network countries.

In almost all PMS Network countries (9/11) there is at least one person responsible for monitoring of AEFI data reported and investigated. It is usually a national focal point from the EPI/AEFI system. Nevertheless, there is no monitoring specifically for AEFI detection and reporting. Monitoring of AEFI reporting is included in the overall monitoring of the immunization programme at the regional (sub-national) level.

In nine countries, the annual number of AEFI cases investigated varied from one to 1545 in 2009 (Figure 9). The data was not available from two countries. The average number of AEFI cases investigated is 252, with standard deviation SD=492 (range 1 to 1545). To make these data comparable, we calculated the number of AEFI cases investigated per 100 000 population of children <5 years, because this age group receives the majority of vaccines from the EPI programme (Table 3). Based on this, one group (3/9) of PMS Network countries had the lowest numbers of AEFI cases investigated per 100 000 population <5 years in 2009 (0.02, 0.14, 0.96, respectively). The second group (3/9) of PMS Network countries had similar numbers of cases investigated per 100 000 population <5 years (1.37, 1.39 and 1.48 cases, respectively) and the third group (3/9) had increasingly higher numbers of cases investigated per 100 000 population <5 years (5.48, 12.66 and 86.61, respectively) during the same year.

Among eight countries which reported annual data from 2007 to 2009, the median proportion of AEFI case investigations that started within 48 hours following reporting was 50%, 51% and 75%, respectively (Figure 10, Table 4).

Among seven countries which reported annual data from 2007 to 2009, the median proportion of preliminary investigation reports available within one week from the start of investigation was 5%, 25% and 50%, respectively (Figure 11, Table 5).

Six countries reported that the majority of final investigation reports (ranging from 50% to 100%) are submitted less than six weeks after the investigation onset.

Among seven countries, the median proportion of AEFI investigation conclusions supported by laboratory findings on clinical specimens, or laboratory findings for vaccine samples, is 10% each, while 62.5% of fatal AEFI cases were supported by post-mortem findings (Table 6).

There is a trend observed in frequency of feedback from the national level to AEFI staff, immunization staff, AEFI reporters and other health-care providers, which is higher compared to parents/vaccinees/community and media groups. In general, countries do not share information with parents and the media.

Monthly or quarterly summary reports of AEFI cases are produced in 10 countries. The information was not available from 1/11 PMS Network country. The annual summary reports are produced in eight countries.

4.3 National immunization safety committee

Ten countries have a national immunization safety committee with responsibilities related either to AEFI case investigation, or to AEFI causality assessment, or to both functions (Figure 12). Usually the committee members are appointed by the Ministry of Health. Four countries have written procedures and criteria for the selection of the members of the national immunization safety committee. Only two countries have written documents with defined roles and responsibilities of the national immunization safety committee.

The frequency with which these immunization safety committees meet ranges from one meeting per month to one meeting every three months; this is confirmed by the existence of the meeting reports among six PMS Network countries.

Eight countries use the WHO classification of AEFI type (vaccine reaction, programme error, etc.). Two countries have country-specific classification of AEFI. Ten PMS Network countries use the WHO categories for causal association with vaccines.

In the majority of PMS Network countries, a routine system is established for review, validation and final categorization by the national immunization safety committee, or by the national AEFI focal points. Three countries reported that a causality categorization is performed by their national immunization safety committee and by the national AEFI focal point(s). Usually, national AEFI focal points are also members of the national immunization safety committee.

4.4 Training

During the telephone interviews we tried to clarify whether updated information, including training materials, are regularly provided at all levels of the AEFI surveillance system. In general, only official documents, decisions and orders relevant to vaccine safety, and issued by MOH, are distributed at almost all levels.

The survey indicated that the median proportion of staff involved in AEFI surveillance that participated in AEFI or related training since January 2006 was >75% (range 0%–100%) at the national level, 63% (range 0%–80%) at the sub-national level and 10% (range 0%–75%) at the health-facility level. Generally, the median proportion of staff trained was correlated with the administrative level in descending order. Consequently, a greater proportion of staff participated from the national level compared to sub-national and health-facility levels, and there was no training reported at health-facility levels. However, this can be biased due to several reasons. First of all, some national focal points were not aware about training conducted at peripheral levels. Secondly, the denominator at sub-national and health-facility level might be greater compared to fewer number of staff working at the national level. As an example, one of the countries reported 100 % of participants from the national level, which was one AEFI focal point at the MOH.

The survey found that the number of trainees who attended AEFI workshops in different countries during a period of three years varied from 15 to 25 000 training participants. We excluded the number of participants at community level (10 000 and 25 000 trainees in two countries) to eliminate skewing of the result. Thus, the average number of trainees in PMS Network countries for the three-year period (2006–2008) was 92 trainees.

Overall, the main groups of participants targeted for training in AEFI workshops were health managers and vaccinators, immunization specialists and epidemiologists, nurses and midwifes, EPI and focal points from different levels, and NRA representatives responsible for post-marketing surveillance at the national and state levels. Workshops for health professionals involved in AEFI surveillance were mostly organized at the national and sub-national levels.

The median proportion of staff from the private sector that participated in training activities since 2006 was 5% (range 0%–60%) among 11 countries. Only one country reported that since 2006 training has involved staff from the private sector; an estimated 60% of trainees. Of the remaining countries, in three PMS Network countries, estimates were that 5% to 10% of staff from the private sector have received training relevant to vaccine safety. Overall, the majority of countries either could not answer this question, or reported that staff from the private sector had not participated in such training sessions.

The information collected is insufficient to describe which type of training has been provided relevant to AEFI. The majority of countries provided general information on training for immunization/AEFI staff, except 4/11 countries, who provided lists describing the training sessions relevant to vaccine safety issues conducted in their countries such as: training for causality assessment provided by WHO; workshops on AEFIs for the focal points and immunization centres; AEFI update at immunization coordinators' meetings; training for national regulatory authority staff on vaccine prequalification and AEFI surveillance (pharmacovigilance of vaccines); seminars at the national level to introduce the national AEFI guidelines, and post-marketing surveillance seminars with training on AEFI monitoring integrated into safe-vaccination workshops.

4.5 Communication with concerned groups

Information, education and communication (IEC)

Four countries have some kind of documentation to provide guidance on the establishment of a communication system relevant to vaccine safety. However, none of the PMS Network countries have prepared documents specific for vaccine safety that can be used as guidance for the establishment of communication systems relevant to AEFI.

Six countries have a communication unit at the national level, which are, in general, responsible for risk communications for the whole public-health system, including vaccine safety concerns.

Seven countries have, at the MOH, a designated spokesperson for media enquiries, who is usually responsible for all public-health issues, including vaccine safety matters. In two PMS Network countries, in case of serious AEFI, one of the committee members or another MOH official may communicate with the media.

None of the 11 PMS Network countries have a communication plan for vaccine safety. However, some information on vaccine safety crisis is included in the national guidelines of a couple of countries.

There is a system among seven countries for providing feedback on AEFI from the national level, mainly to the health-care providers and occasionally to the media. No process for providing feedback to the community was documented or demonstrated by any of the countries.

In six countries, either EPI or NRA regularly checks the local media for reports of AEFI.

Different countries responded differently on the existence of information materials for the community and for parents and vaccinees. Eight countries have information materials relevant to vaccination for the community, and for parents and vaccinees.

Limited information is provided on vaccine safety issues to parents and community members. Five countries do not have information materials on vaccine safety for both concerned groups.

Seven PMS Network countries do not share information on vaccine safety and AEFI with the private sector. Only in countries where the NRA collaborates regularly with the private sector is information relevant to vaccine safety provided to representatives of the private sector.

Six PMS Network countries have conducted IEC sessions on immunization for mothers during the last three years. Usually, in those countries which do not conduct the IEC sessions for parents, the health-care workers provide parents with explanations about vaccines and possible vaccine reactions, prior to immunization sessions.

4.6 Vaccine utilization

Information on the total number of doses distributed is recorded at the national level in 10 countries.

The information on lot/batch number of doses distributed is recorded at the national level in nine countries. There is a tendency to record lot number of doses distributed at higher supervisory levels compared with health-facility level. Consequently, trends observed in this survey suggest that the probability of finding information on lot/batch number of doses distributed is higher at the national level compared to sub-national and health-facility levels. This is logical, as vaccines are distributed from the national to lower supervisory levels, and therefore the information on distribution of vaccines is likely to be recorded at higher supervisory levels. However, it is important to record lot/batch numbers at health-facility levels as well, so as to permit easy identification of lot/batches during AEFI investigations and follow up of cases.

The information on total number of doses administered is recorded and available at all levels in 10 countries. This is a good indication in case of tracing information on vaccines associated with AEFI cases and is also used for denominator data to allow for reliable estimation of coverage.

The information on lot/batch number of doses administered is recorded less often compared with number of doses distributed and administered, hence, this information is submitted to the national and sub-national levels in only five countries.

The data collected for vaccine utilization was consistent with information collected previously during the CP survey.

Appendix I:

Table 1: General overview of key findings

I. STRUCTURE AND MANAGEMENT OF AEFI SYSTEM		NETWORK COUNTRIES **										
		1	2	3	4	5	6	7	8	9	10	11
1	Responsible institution(s) for AEFI reporting	EPI	EPI/NRA*	EPI	EPI/NRA	EPI	EPI/NRA	EPI/NRA	EPI	EPI/NRA	EPI	EPI
2	Designated national focal point for AEFI surveillance					Not officially designated					WHO seconded	
3	Existence of National Pharmacovigilance Centre			At national level		Substitute institution						
4	Collaboration between EPI and NRA		Active collaboration	NA	Active collaboration		Active collaboration			Active collaboration		
5	Existence of national AEFI surveillance guidelines											
6	Dissemination of guidelines to staff at all levels				2 levels							
7	Documented roles and responsibilities of key players											
II. AEFI SURVEILLANCE FUNCTIONS (AEFI reporting and data management)		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
8	Existence of standardized AEFI reporting forms											
9	Existence of the list of AEFIs eligible for reporting	WHO	Orientation list	WHO	WHO			NO	WHO	Not clear	WHO	
10	Distribution of the list of reportable AEFIs		2 levels					?				
11	Existence of current AEFI case definitions			WHO	WHO		BC		WHO		WHO	WHO
12	Distribution of the current AEFI case definitions											

Table 1: General overview of key findings *(cont'd...)*

13	Existence of written procedures (SOPs) for AEFI reporting and case management	Substitute document										
14	Specified time frame for reporting serious AEFIs	24–48 hours	24 hours	24–48 hours	24 hours	24 hours	24–48 hours	24 hours	24 hours	24–48 hours	24 hours	24–48 hours
15	Specified time frame for reporting NON-serious AEFIs	Weekly	Monthly	Monthly	Monthly		Monthly	Weekly			Monthly	Monthly
16	Use of case-based data reporting											
17	Use of line-listing tool											
18	Use of aggregated data reporting											
19	Data coding/entry performed (at national level)											
20	Database manager(s)											
Case investigation and analysis		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
21	SOPs for case investigation available at national level											
22	Existence and distribution of case-investigation forms at all levels											
23	Existence of case- investigation reports											
24	Monitoring of peripheral levels for AEFI reporting and investigation											

Table 1: General overview of key findings *(cont'd...)*

III. NATIONAL IMMUNIZATION SAFETY COMMITTEE		1	2	3	4	5	6	7	8	9	10	11
25	Existence of immunization safety committee	Investigation	Causality	Both	Causality	Causality	Both	Both	Both	Both	Rapid team	Both
26	Existence of written procedures and criteria for the selection of the members of the national immunization safety committee											
27	Documented roles and responsibilities of the national immunization safety committee(s) members											
28	Existence of the meeting reports of regular meetings of AEFI committee											
29	Written procedures (SOPs) for case investigation of SAE or cluster events											
30	Use of classification of AEFI type (vaccine reaction, programme error, injection reaction, coincidental)		N,S,H***	N,S	N,S,H			N	N	N,S	N	N,S
31	Use of the WHO categories for causal association with vaccine(s) (very-likely/certain, probable, possible, unlikely, unrelated and unclassifiable)						Only COFEPRIS (NRA)					
IV. TRAINING		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
32	Updated information on AEFI surveillance provided at all levels		N,S	N,S,H	N,S,H	N	N,S,H	N,S,H	N,S,H	N,S	N,S,H	N,S,H
33	Training provided for staff involved in AEFI surveillance since 2006											
34	Training on AEFI surveillance provided for private sector since 2006			N/A	N/A	5%	60%	10%		5%		NA

Table 1: General overview of key findings *(cont'd...)*

V. Communication with concerned groups		1	2	3	4	5	6	7	8	9	10	11
35	System for providing feedback on AEFI											
36	Document that provides guidance on establishment of a communication system/plan relevant to vaccine safety/AEFIs									Newsletter		Poster
37	Existence of communication unit at national level responsible for communication with concerned groups on vaccine safety/AEFIs											
38	Designated spokesperson for media enquiries relevant to vaccine safety or AEFI	Committee member				Committee member	NRA					
39	Written communication plan in case of vaccine safety crisis											
40	Frequency of sending results of AEFI investigation and analysis to reporters at peripheral level	Occasionally	Occasionally	Almost always	Almost always	Often	N/A	N/A	Often	Occasionally	Almost always	Never
41	Frequency of sending feedback to community and parents/vaccinees	Almost never	Almost never	NA	Almost never	Occasionally	NA	NA	Almost never	Occasionally	Almost always	Often
		1	2	3	4	5	6	7	8	9	10	11
		NETWORK COUNTRIES **										

* The information inserted in some boxes is for clarification, if different from other responses, or if responses are heterogenic.
** The names of 11 PMS Network countries are substituted by numbers from 1 to 11.
***N, S, H: National, Sub-national and Health facility levels

From this table it is possible to get a general overview of the answers to the questions considered as the indicators for minimal capacity.

Legend for Table 1:

- YES - YES, but differing from main responses - NO

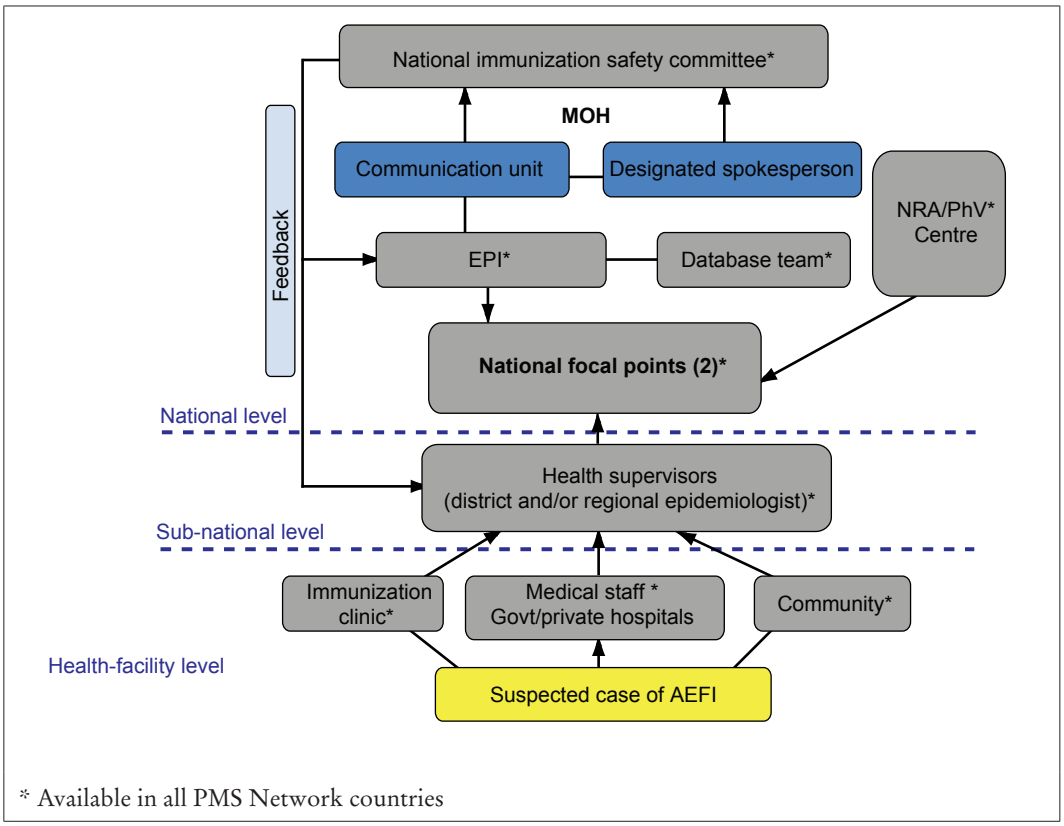
Appendix II:

Table 2: Responsible institutions for AEFI reporting

EPI	EPI and NRA	Total
6	5	11
1, 3, 5, 8, 10, 11	2*, 4, 6, 7, 9**	

* In country two - public sector reports to EPI, and private sector to NRA;
** In country nine - national centre of pharmacovigilance, NRA is responsible for private sector, while both EPI and NRA have joint responsibility for public sector.

Figure 1: Generic AEFI reporting flow chart is based on flow charts provided by 11 PMS Network countries. The blue boxes with * are common elements for all PMS Network countries



* Available in all PMS Network countries

Figure 2: Existence of written procedures (SOPs) for AEFI reporting and case management

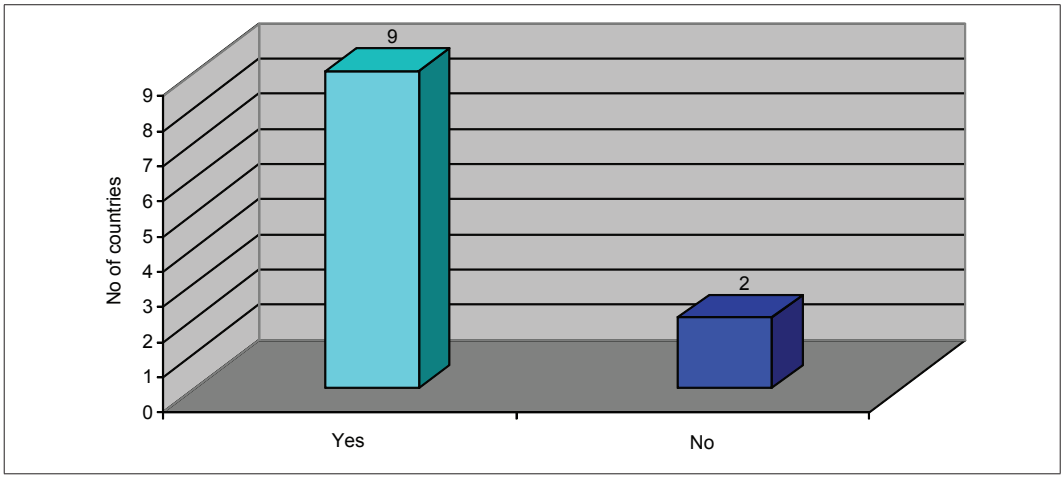


Figure 3: Specified time frame for reporting serious AEFIs

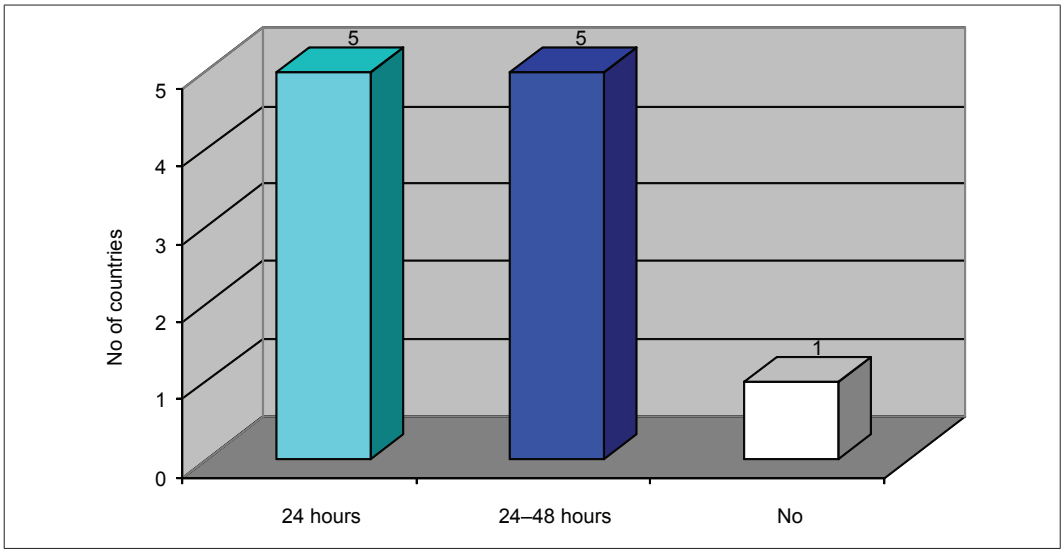


Figure 4: Usual timelines for reporting non-serious AEFIs

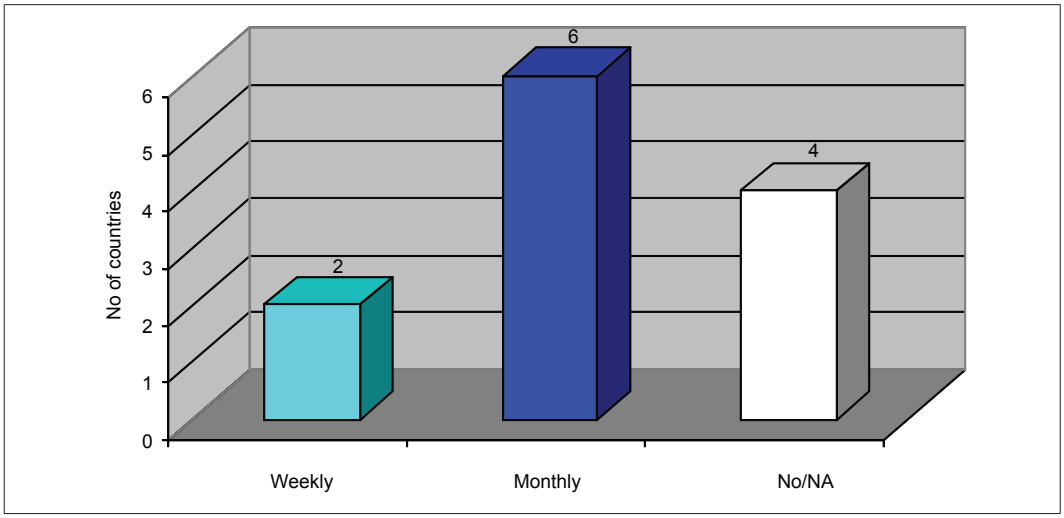


Figure 5: Mandatory to report serious AEFIs

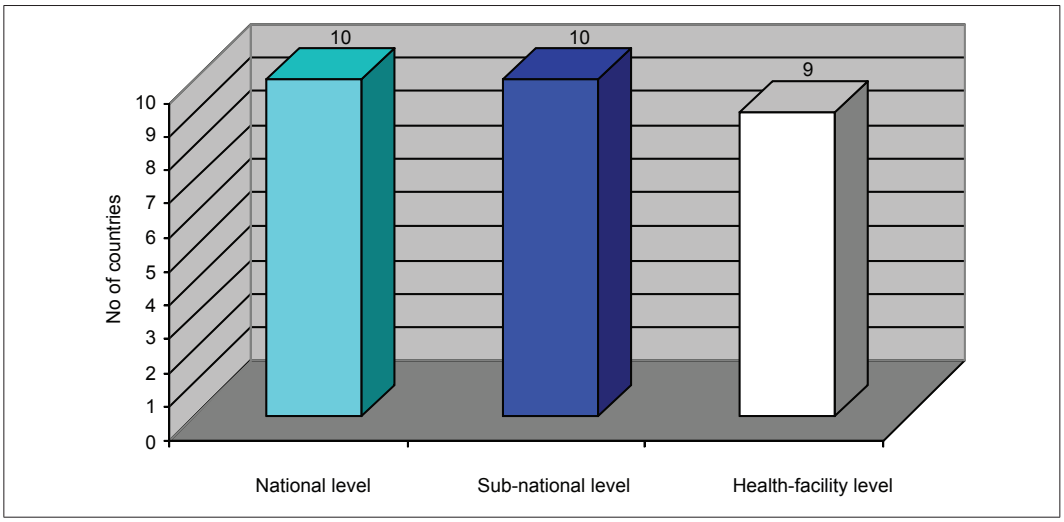


Figure 6: Mandatory to report non-serious AEFIs

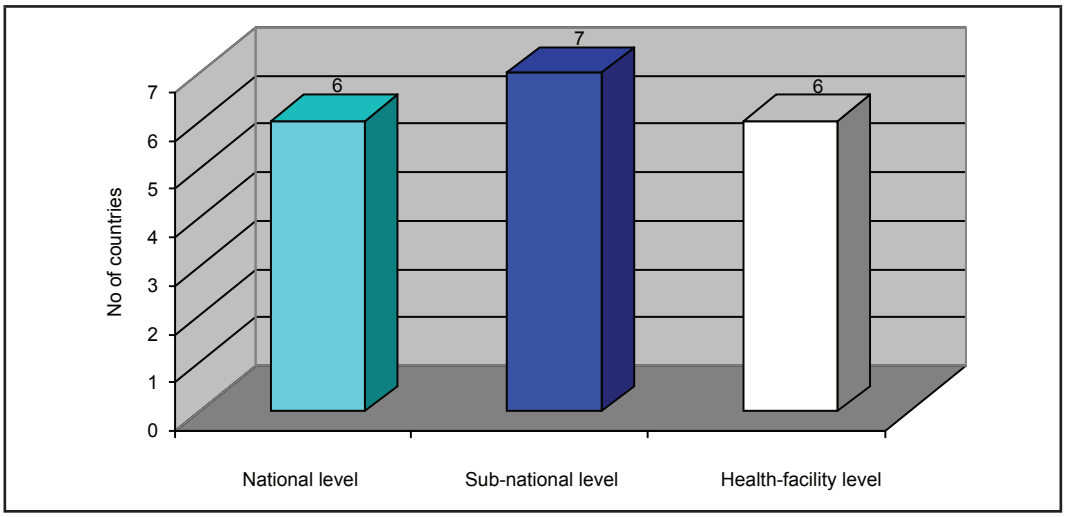


Figure 7: Type of tool used for AEFI reporting

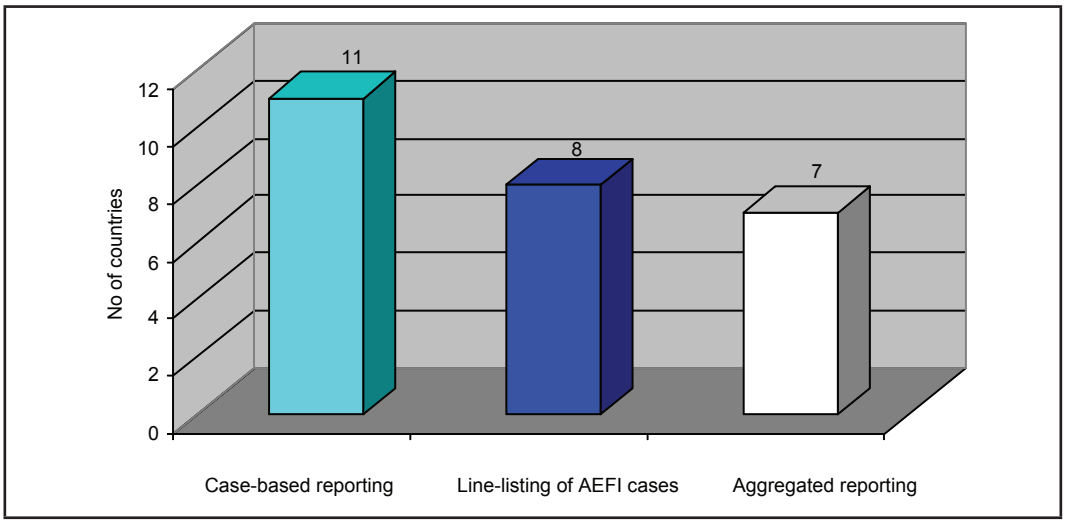


Figure 8: SOPs for AEFI case investigation

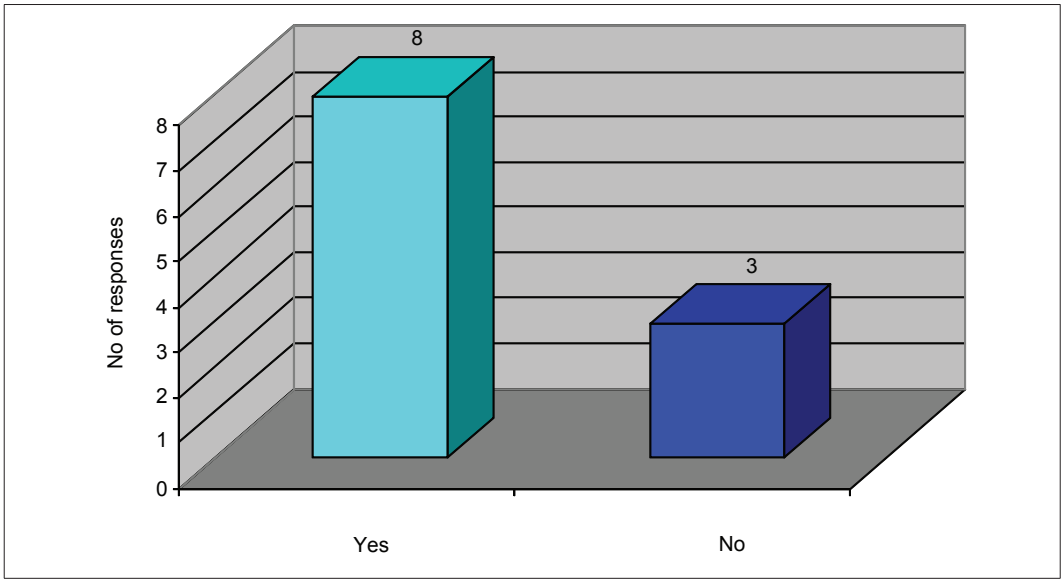


Figure 9: Number of AEFI cases investigated in 2009

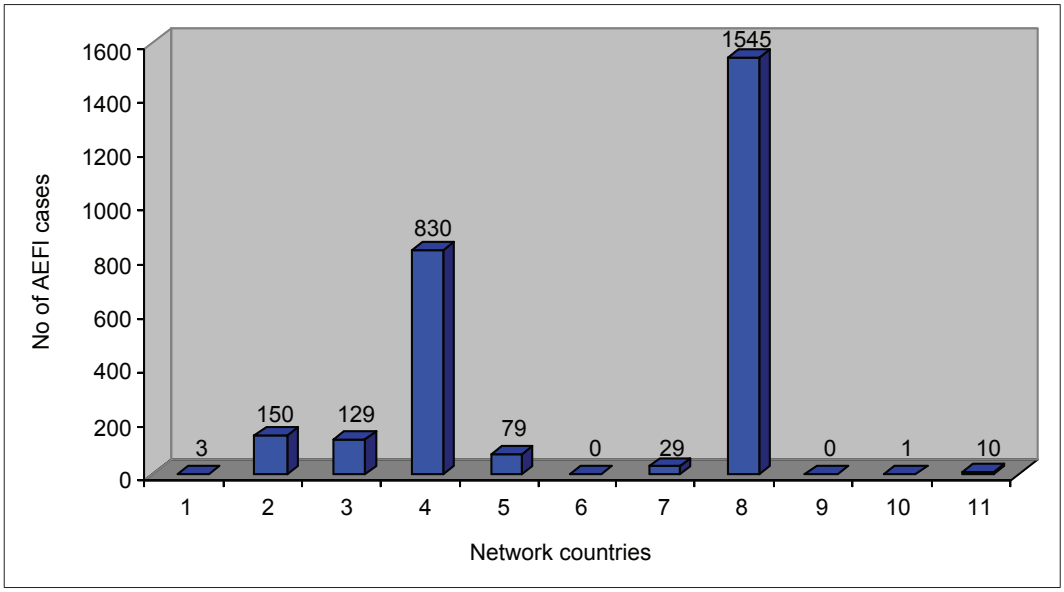


Table 3: Number of AEFI cases investigated per 100 000 population of children under 5 years of age in 2009

Countries*	Number of AEFI cases investigated in 2009	Population of children <5 years of age	Number of AEFI cases investigated per 100 000 population of children <5 years of age
1	3	219 489	1.37
2	150	15 654 687	0.96
3	129	8 697 079	1.48
4	830	6 554 616	12.66
5	79	1 440 969	5.48
6	NA	NA	NA
7	29	2 093 807	1.39
8	1545	1 783 778	86.61
9	NA	NA	NA
10	1	6 368 078	0.02
11	10	7 238 286	0.14
Mean	252		

* The names of 11 PMS Network countries are substituted by numbers from 1 to 11.

Figure 10: Proportion of AEFI case investigations started within 48 hours following reporting in last three years

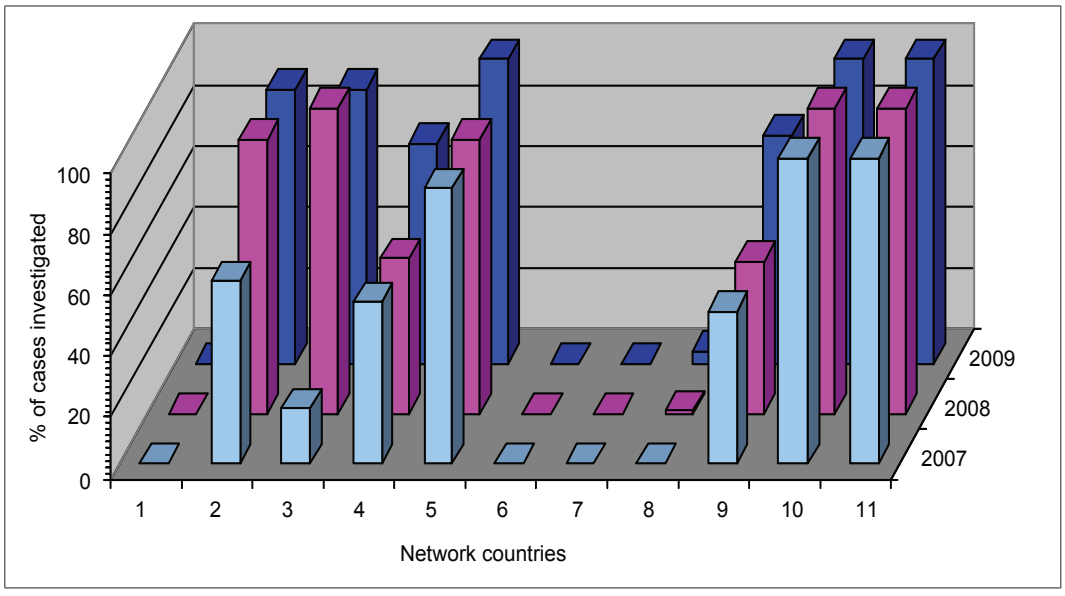


Table 4: Median proportion of AEFI case investigations started within 48 hours following reporting in last three years

Network countries*	2007	2008	2009
1	0%	0%	0%
2	60%	90%	90%
3	18%	100%	90%
4	53%	51%	72%
5	90%	90%	100%
6	0%	0%	0%
7	0%	0%	0%
8	0.1%	1.0%	4.20%
9	50%	50%	75%
10	100%	100%	100%
11	100%	100%	100%
Median	50%	51%	75%

* The names of 11 PMS Network countries are substituted by numbers from 1 to 11.

Figure 11: Proportion of preliminary investigation reports available within one week from the start of investigation for 2007–2009

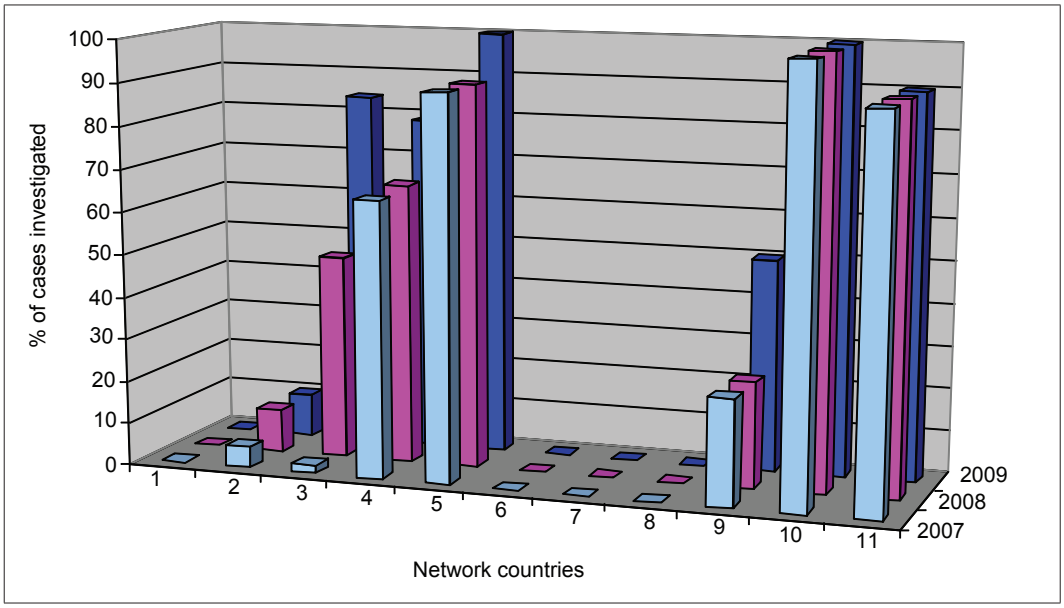


Table 5: Median proportion of preliminary investigation reports available within one week from the start of investigation during 2007–2009

Network countries*	2007	2008	2009
1	0%	0%	0%
2	5%	10%	10%
3	2%	48%	84%
4	65%	66%	79%
5	90%	90%	100%
6	0%	0%	0%
7	0%	0%	0%
8	0%	0%	0%
9	25%	25%	50%
10	100%	100%	100%
11	90%	90%	90%
Median	5%	25%	50%

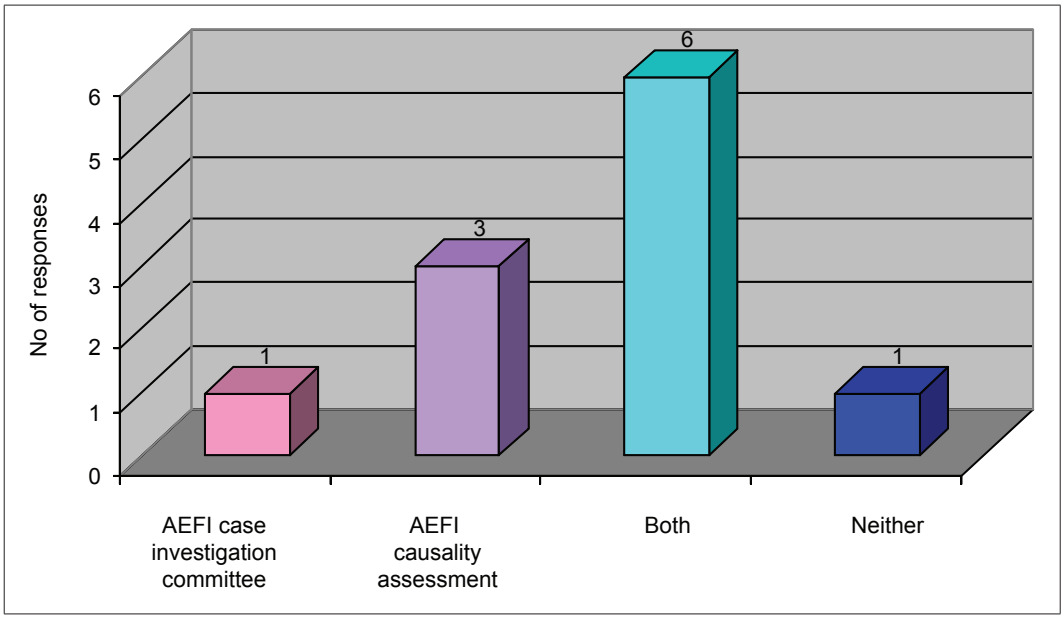
* The names of 11 PMS Network countries are substituted by numbers from 1 to 11.

Table 6: Median proportion of AEFI investigation conclusions supported by laboratory findings

Network countries*	Laboratory findings (positive or negative) on clinical specimen(s)	Post-mortem findings (among AEFI deaths)	Laboratory findings (positive or negative) for vaccine samples
1	No experience with such cases		
2	>=75%	10% to <25%	<10%
3	25%–50%	>75%	10%–25%
4	NA	NA	NA
5	10%	10%	10%
6	NA	NA	NA
7	NA	NA	NA
8	<10%	>75%	<10%
9	NA	100% for death	NA
10	<10%	0%	<10%
11	Very limited	<50%	Do not send
Median	10%	62.5%	10%

* The names of 11 PMS Network countries are substituted by numbers from 1 to 11.

Figure 12: National immunization safety committee(s)

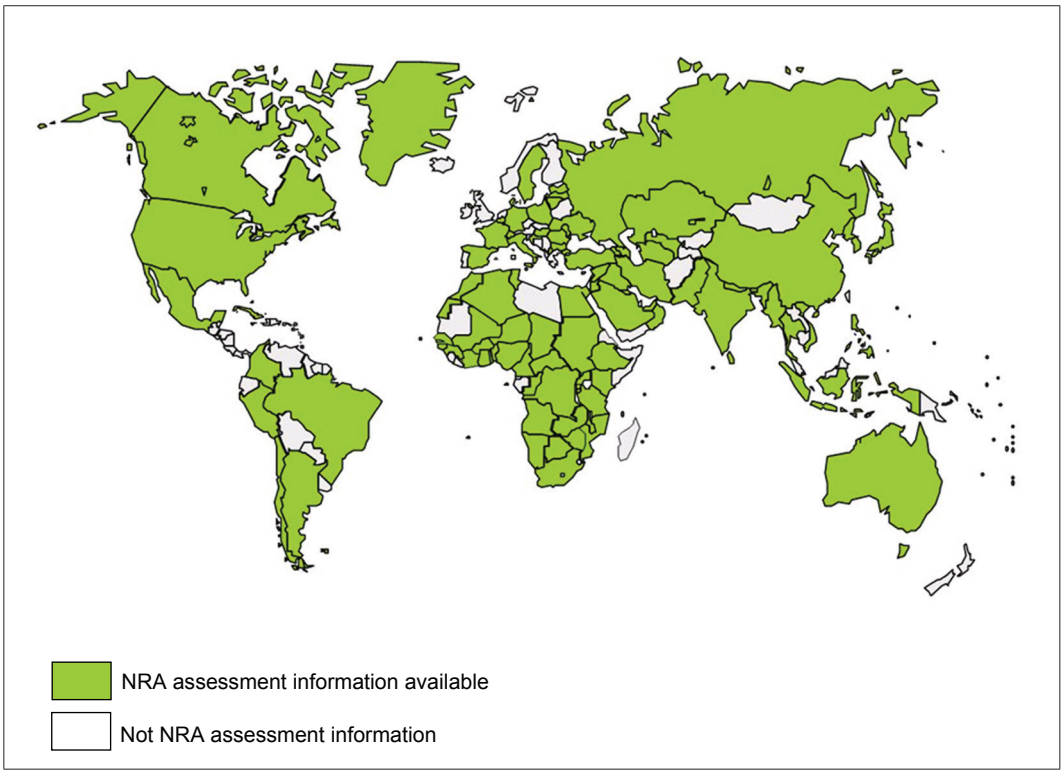


Analysis of NRA assessment data

1. Background and context

Between September 2009 and December 2010 (15 months) an analysis of the data gathered from all national regulatory authority assessments that were conducted in 101 countries were analysed, with a focus on post-marketing surveillance, including the adverse events following immunization (PMS/AEFI) surveillance function. These data were analysed in two phases. The first phase data were presented during the July 2010 retreat of the WHO global safety blueprint in London. The second phase of analysis that was planned, taking into consideration the comments provided during the retreat, was completed in early January 2011.

Figure 1: Strengthening national regulatory authorities — 101 countries assessed and/or followed up as of 2009



The main findings provide information on the following aspects: existence of a system; its level of implementation; its documentation to be implemented consistently to WHO recommendations, to plan, run and monitor the PMS/AEFI surveillance programme; the coordination and exchange of information between the key stakeholders and institutions; the data management and monitoring; the vaccine performance framework; the feedback to relevant institutions, inside or outside the country; training of health staff and professionals; the capacity to detect and investigate in a timely manner, monitor completeness and analyse the information and detect signal, including causality management, and regulatory oversight of manufacturers for PMS.

The analysis reviewed the global picture, according to WHO regions, and group of countries according to level of income, health expenditures, diphtheria-pertussis-tetanus (DPT3) immunization coverage and UN Human Development Index (HDI). All eight PMS/AEFI indicators were compared against these indicators. The analysis focused mainly on the indicators and not on all the sub-indicators, as only selected sub-indicators was drawn to be analysed during the review.

The analysis was lead by WHO quality safety standards teams of the Department of Immunization, Vaccines and Biologicals, and several experts and data managers (including one IT staff) were also involved. Country experts that were invited to contribute to the review process through drafting, analysis or comments were recruited from the following countries: Senegal (AFR), Brazil (AMR/PAHO), India, Sri Lanka (SEAR), the Islamic Republic of Iran, Tunisia (EMR). In addition, WHO staff involved in PMS/AEFI activities, from WHO Headquarters, WHO South-East Asia Region, WHO European Region and WHO Western Pacific Region, were also invited to provide comments.

The main findings can be divided into: (a) global analysis; (b) regional analysis; (c) economic, access and composite indicators. Since 1996, WHO has collected data through 315 country visits and 101 WHO assessments of the vaccine regulatory systems that were conducted in all regions of the world (Figure 1). So far, WHO has been able to document the situation against a set of indicators in all the regulatory systems assessed (101). These data concern all various regulatory functions ranging from: system components; marketing authorization and licensing activities; post-marketing surveillance (PMS) of AEFI; NRA lot release; laboratory access, and regulatory inspections and oversight of clinical trials. For each of these functions, WHO is routinely analysing the information and providing, through a dedicated website, the outcome of these analyses for planning purposes. Some funding was already provided from the GAVI Alliance to focus on GAVI countries that were supported from their grant, and to develop specific databases. This report focuses on the indicators and sub-indicators relevant to the PMS/AEFI.

The WHO NRA assessment tool consists of a composite scale to transfer sub-indicators and indicators to a measurable term; hence it allows a comparison of performance by each function over a time period to illustrate the progress of the NRA system.

Description and assumptions are:

- a description of the status of the PMS/AEFI regulatory functions in all countries assessed by WHO (functional, not functional, low/medium/high maturity level);
- a description of the eight indicators and their status for each country assessed from 1996 to 2008, as described in Table 1.

Table 1: Indicators for the post-marketing surveillance (PMS) of adverse events following immunization (AEFI)

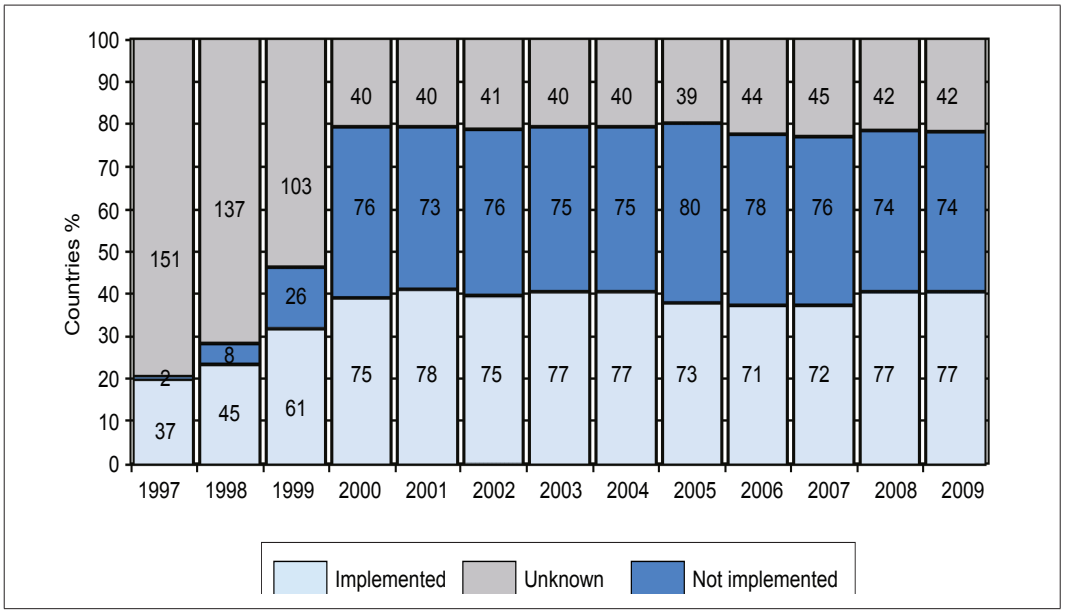
Indicator number	Aspect evaluated
PM1	Institutional regulations and guidelines for post-marketing surveillance, including monitoring and management of AEFI
PM2	Quality management system for post-marketing activities
PM3	Roles and responsibilities of the key players (immunization staff, NRA, NCL, surveillance staff, etc.)
PM4	Human resource management
PM5	Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action, including a process to review and share relevant data between key players, and taking appropriate action
PM6	Capacity to detect and investigate significant vaccine safety issues
PM7	Regulatory outcome regarding vaccine performance
PM8	System for providing feedback on AEFI from the national level to all levels

2. Results

2.1 Global analysis

The PMS/AEFI 1997–2009 NRA function implementation status (Figure 2) illustrates progress in documenting country performance over time, with 35 countries (18%) having implemented the function in 1997, to 77 (35%) in 2009. At the time of the analysis, following 356 country visits, 35% of the countries of the world have implemented NRA function. For the remaining 65%, 32% were not implemented and 33% are unknown. In general, almost all indicators show slow and gradual, but positive progress, on combined partial/full implementation of indicators and sub-indicators. Figure 2 below shows progress at the level of all eight indicators.

Figure 2: Status of PMS/AEFI function 1997–2009

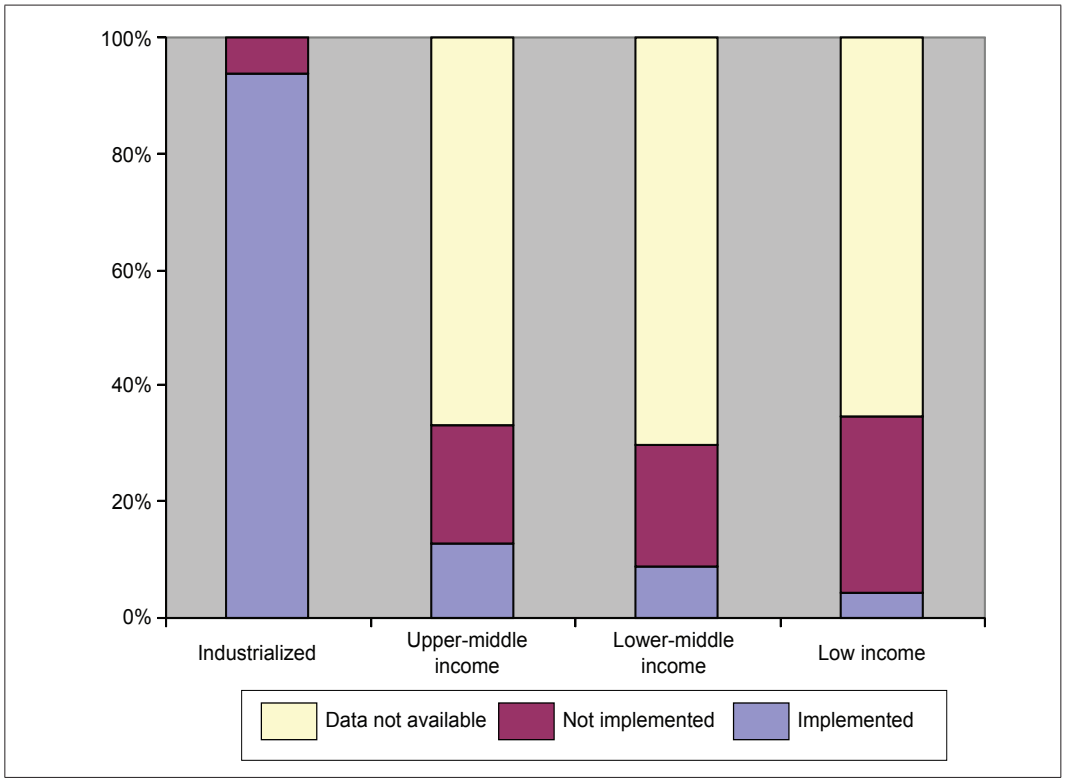


2.2 World Bank economic status

The comparison was based on the income allowed to differentiate two major groups: (1) industrialized countries which were all assessed against WHO NRA indicators and for which the percentage of countries that met the indicators ranged between 90% to 100%; (2) all middle- and low-income countries for which the percentage of implementation of those with data available ranges between 23% to 54%. Currently, if we exclude industrialized countries, only 30% middle-, low middle- and low-income countries were assessed against indicators. This is explained because the WHO priorities to conduct assessment were mainly targeting (a) vaccine producing, and (b) procuring countries, that are ranged in the group of industrialized and middle-income countries.

Industrialized countries have higher scores in implementing all indicators. The analysis also shows that a range of 43 to 48, out of 48 industrialized countries, have implemented all the indicators of the post-marketing activities, including surveillance of AEFI function. They are closely followed by upper middle-income and lower middle-income countries which have similar results, and then by the group of low-income countries. Figure 3 illustrates data available on PM06 that documents the capacity to detect and investigate significant vaccine safety issues. If we consider the level of implementation between the middle income and the low- income countries, it is usually about 2-fold higher, except for the last indicator (PM8 – system for providing feedback on AEFI from the national to all levels), for which the ratio is closer to one that indicates that country economic status makes a major difference in implementing the PMS/AEFI function and relevant indicators.

Figure 3: Indicator PM6 according to World Bank economic status

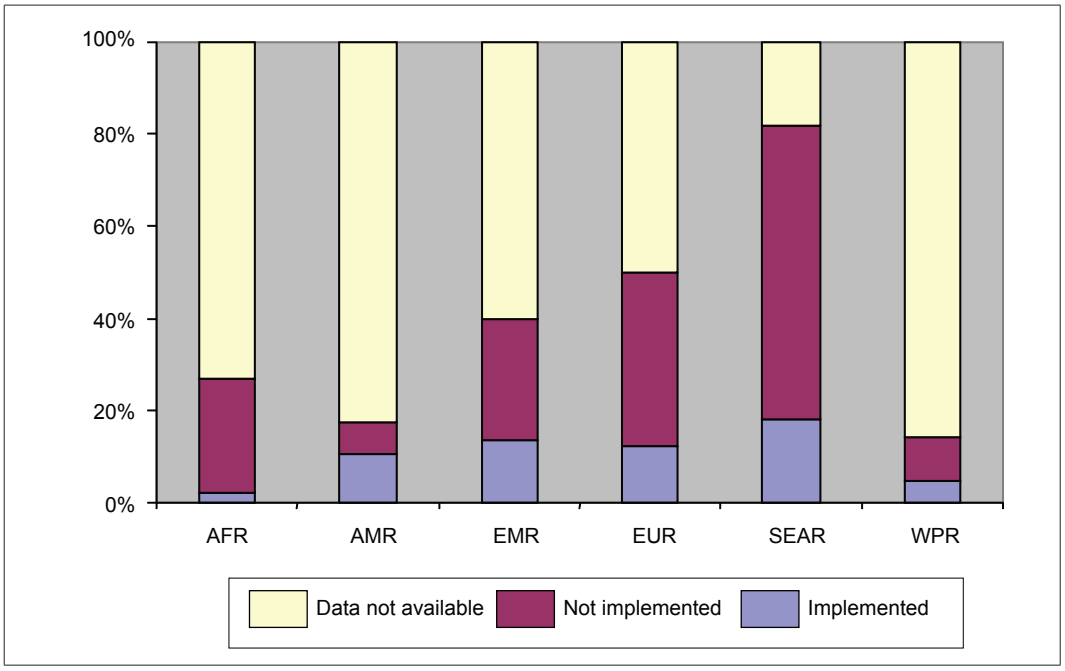


2.3 WHO regions

The performance of implementation by WHO regions indicates that the WHO African Region, Region of the Americas and Western Pacific Region, have a low implementation of the AEFI/PMS indicators, with a percentage generally under 10% out of the total countries in each region. This percentage is, in part, explained by the low number of countries from these regions that were assessed (27%, 17% and 14%, respectively).

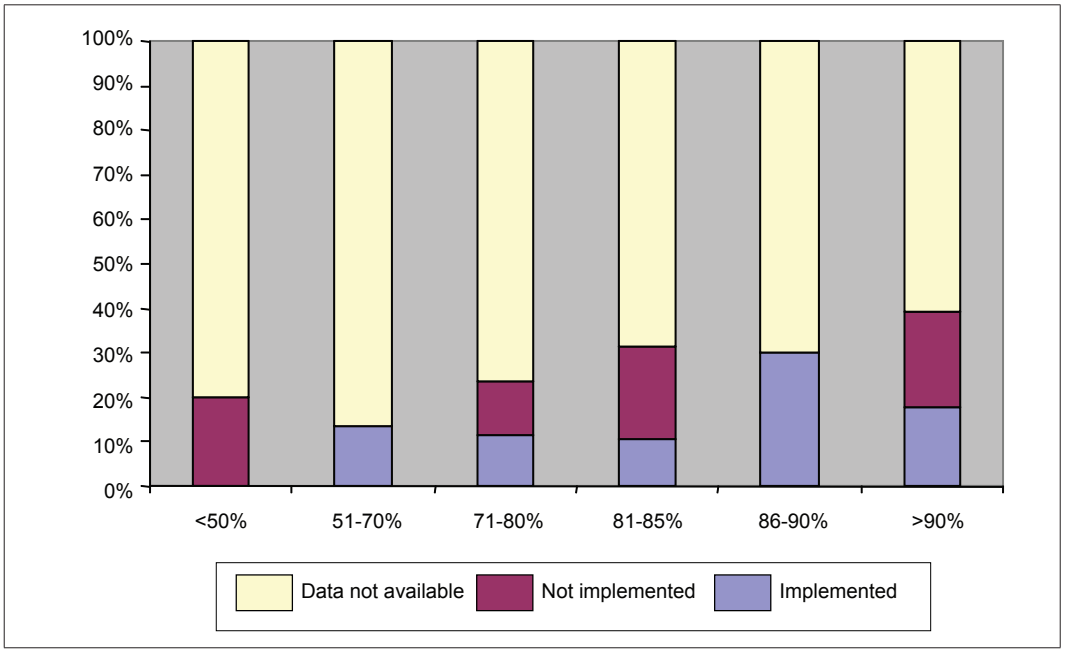
On the other hand, in the South-East Asia Region, 82% of countries have data available. In the South-East Asia Region, the percentage of implementation for these countries ranges between 22% (PM6) to 56% (PM3, PM4 and PM5). Countries from the Eastern Mediterranean Region have implementations ranging between 13% and 33%, and for the European Region, 8% to 38%. In the European Region, countries that had low implementation are mostly all former computerized EPI information system/national immunization survey (CEIS/NIS) countries that faced serious organizational and resources issues. The group of countries in the European Region that have implemented the function are the old and new European Union countries (27 countries); however, within this group, some countries are not meeting high levels of performance, since they had joined the European Union recently, and are still developing their PMS/AEFI programmes. Figure 4 illustrates data available for PM6.

Figure 4: Indicator PM6 by WHO region (excluding industrialized countries)



2.4 DPT3 immunization coverage

Figure 5: Indicator PM6 by DTP3 coverage (excluding industrialized countries)



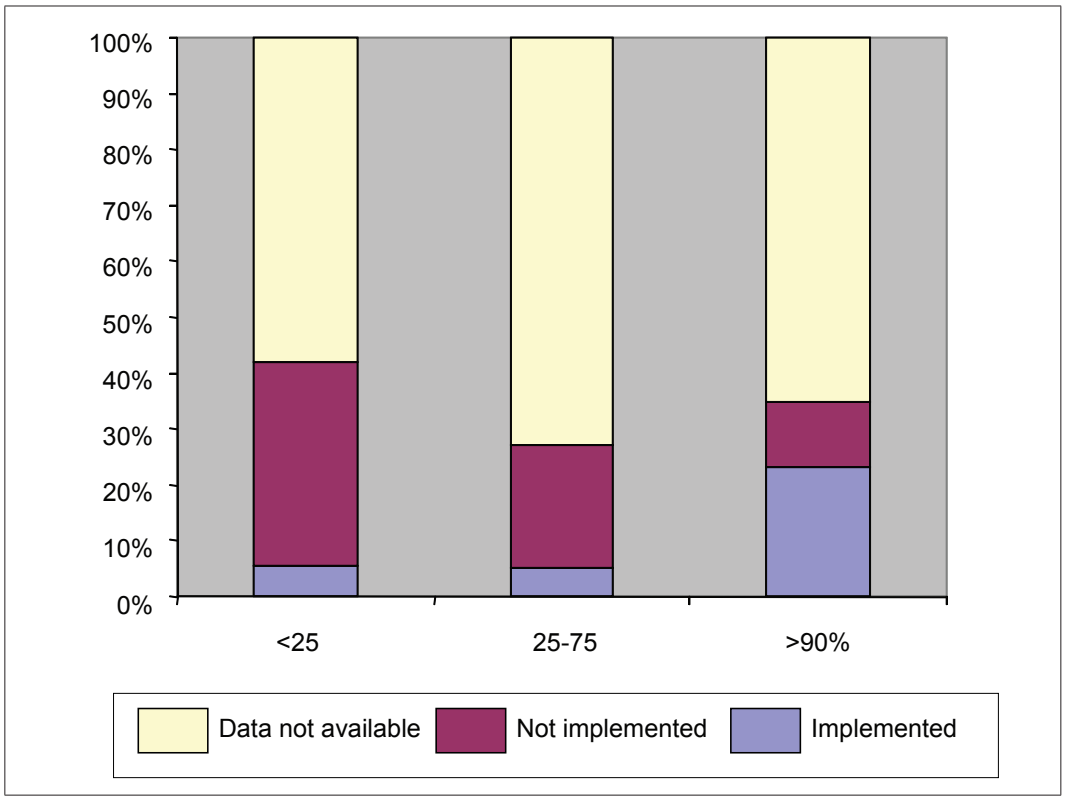
Countries with a DTP3 coverage ranging between 86% and 90% had implemented the indicators with the highest percentages; up to 100% if we consider only those with data available (and up to 30% if it is calculated using the total number of countries). This group is followed by the one with a DTP3 coverage >90%, which is the largest group (79 countries), including up to 17 countries which have implemented the indicators, out of 31 with data available, and out of 79 of the total number of countries.

The implementation of the indicators according to coverage reflects the correlation between the performance of immunization services and the health system in general. New assessments would refine the results and allow a more accurate analysis. In addition, it would be interesting to reassess those countries with a DTP3 coverage >90% to identify issues, and to assist them in implementing the indicators. Figure 5 illustrates data available for PM6.

2.5 Health expenditure

The largest group of countries (81) is represented by those for which health expenditure is ranged between US$ 25 and US$ 75 per person per year. The group of countries with the highest health expenditure (US$ >75 per person per year) performs definitively well and reaches high percentages. In general, the group of countries for which the health expenditure is US$ <25 achieved better percentages than the second group (health expenditure between US$ 25 and US$ 75). This suggests that post-marketing activities, including surveillance of AEFI function, does not require high investment to have an impact on programmes and on the relevant health-system component, but it seems to be more dependent on the effectiveness of the programme's management of activities.

Figure 6: Indicator PM6 by health expenditures (excluding industrialized countries)



2.6 UN human development indicators (HDI)

The HDI measure is a composite indicator that measures governance, social-, health-, education- and economic-development in terms of life expectancy, educational attainment and adjusted real income. This index has not been calculated for 22 countries that were included in the sample for 2010, because of missing information.

The implementation of the indicators seems to match the rank assigned for the HDI. Countries with a very high HDI confirm they have achieved higher performance, close to 100%, of those with data available, and all these countries already represent 50% of the total countries assessed in each region. This group is followed by both groups of countries with a high HDI and a middle HDI, for which 18% to 29% of the total countries in each region have implemented the indicators PM1 to PM5. The indicators PM6 to PM8 have been implemented by a lower percentage of countries among these regions; 11% to 13% out of the total countries in the region. Only a few countries (1–4) from those with a low HDI have implemented the indicators.

3. General conclusions

The results of this study show that most industrialized countries (90% to 100%) have implemented the PMS/AEFI indicators. However, there is a need to strengthen the regulatory PMS/AEFI function in most middle- and low-income countries and, more specifically, in the countries that are in the following subgroup.

a) Health expenditure US$ <75 per person per year.

b) DTP3 coverage <86%.

When looking at the HDI and the level of performance of each PMS/AEFI indicator, we can see a correlation between the level of HDI and the level of performance of the indicators. This also suggests that it will be interesting to investigate further to see which composite indicators of the HDI might influence the highest development of PMS/AEFI performance and its sustainability.

When observing the percentages of implementation of the indicators between different groups, we found similar profiles between both indicators PM2 and PM3 and, in some cases, between PM1 and PM2. Indeed, the establishment of the quality management system (PM2) requires both the existence of written guidelines (which is part of PM1) and the definition of responsibilities (which is also requested with the indicator PM3).

Data also confirm that PMS/AEFI is linked to the economic status; wealthy countries can do more than poorer ones in developing their PMS/AEFI system. However, for activities relevant to indicators PM1, PM4 and PM5, a greater proportion of lower middle- income countries than those with an upper middle income had met the indicators; one reason being that there are national plans to develop, build capacity and monitor the activities and, in several cases, these plans had contributed to mobilize national and external resources for the programme, and increase political commitment and support.

The relationship between health expenditure and the implementation of the indicators seems to be less obvious. This suggests that the implementation of the function does not require too much investment, although WHO estimates of minimum spending per person per year needed to provide basic, life-saving services, is ranged between US$ 35 to US$ 50. It is also noted that, when launching a PMS/AEFI programme, few activities need to be implemented that are focusing on setting a national framework to build capacity (national guidelines, assigning a focal point and institution, etc.), than when activities needed to further expand more funding is definitively required, as more institutions and staff are involved in the system. Funds should be used more efficiently by countries (especially by the group of countries where health expenditure is between US$ 25 to 75 US$ per person per year), and assistance could be provided by WHO to help them to achieve this objective with a minimum level of external resources.

These preliminary results give a global vision of the status of the PMS/AEFI surveillance activities and recommend the definition of new priorities, as well as investment in better planning (institutional development plan to guide countries to coordinate and optimize use of existing resources) when combining the parameters which were used to realize this study. For instance, low-income countries from the WHO African Region, with health expenditure between US$ 25 to US$ 75 per person per year, and a DTP3-coverage between 71% and 80%, may point a way to optimize the current programme and guide priority for investment.

4. Recommendations for country capacity and further analysis

Data from this analysis also points to framing requirements for minimal capacity for vaccine safety at country level. Concepts and principles to guide countries to establish, develop and sustain a vaccine safety programme, can be derived to help the vaccine safety blueprint project further develop the concept and its implementation. The analysis shows that:

- Legal frameworks that enable the development and implementation of the recommended functions exist in all industrialized and middle-income countries. However, they do not exist at all, or are limited, in low-income countries. Further support for the establishment of a minimum legal framework would therefore be an important component to support national governance and build the minimal capacity to further develop a vaccine safety programme in all low-income countries.
- Detection of signal through active reporting does not exist in most of the countries; however, it exists as spontaneous reporting in most countries but is not often used optimally to detect signals and take appropriate actions, whatever the level of income. The project should refine or propose acceptable definitions to be able to further analyse the information available, and to clarify what would be desirable in terms of active surveillance capacity.
- Current scientific investigation mechanisms, that may exist at country level, with resources available or with external support, is documented through the survey as established in all industrialized countries without external support, and in most middle-income countries with occasional external support. The analysis also indicates that the samples of middle income- and low-income countries that were assessed was limited to 30% of the total. The limited amount of data currently available may limit the extrapolation of the analysis to all countries of this group. Further assessment may be recommended to confirm the preliminary findings in these countries.

- Capacity to initiate timely corrective actions when concerns and established risks are investigated and documented, is in place in all industrialized countries, and some high income- and middle-income countries. For these countries, the system performs with some differences in some middle-income countries that may not have all the necessary expertise, particularly in the introduction of new products. Overall, there are coordination mechanisms between stakeholders and a monitoring of the safety concerns where the regulatory system for vaccine safety is established and functioning. In all these countries, a documented system exists that aims to meet the guiding principle of a quality management system.
- In the area of communication of concerns and establishing risks locally with international partners (assessed through vaccine performance and feedback indicators), networks that share information to the public, through websites and other communication channels, are available in industrialized countries and some middle-income countries. In the low middle- and low-income countries, communication systems are limited, usually with no communication strategy for the public, media and other relevant international or interested partners or agencies. This reflects the limited infrastructure, staffing and financial resources, and lack of a system-development plan in these countries.
- All countries assessed operate through a direct supervision of the Ministry of Health, and most institutions, if not all, are under national-health service coordination mechanisms, often represented by the Ministry of Health. There is almost no private-sector involvement in this process, except when vaccine manufacturers have their own PMS systems.
- Access to expertise was also documented through defined responsibilities of relevant stakeholders and access to expertise in the area of vaccine safety. The indicators show higher performance in all industrialized countries and in middle-income countries. However, it remains limited in the area of new vaccines. Many regulatory agencies have a limited interest in vaccines, focusing primarily on pharmaceuticals. A greater emphasis on vaccine production, vaccine safety and quality, and vaccine development is therefore required, in order to better understand issues around the introduction of new vaccines that will often be complex products.
- The existence of a regulatory framework was documented through indicator PM1 and PM2. Data indicate a strong legal framework with specialized and documented process in all industrialized countries, the majority of middle-income countries and quite a significant number of low-income countries. However, in this group, the regulatory framework is usually less developed and primarily provides a mandate to the programme.
- Most industrialized countries have a strategic planning process that covers several years, between two to five years and, in some cases, more than 10 years. All countries have a one to five-year workplan that includes performance indicators to monitor progress. A major difference between industrialized countries and low-income countries is the level of monitoring and supervision of the implementation, which is weaker in low-income countries. Industrialized countries often have a strong qualified management system that may be resource-intensive and costly. Moreover, performance indicators are not used to drive strategic planning after the plans have been developed.

Financial assessment

Executive summary

The goal of the study was to provide data on the cost and funding for; (a) current vaccine safety systems in low- and middle-income countries (LMICs), and (b) international vaccine safety initiatives. These data were collected to inform decisions on budgets and funding choices for WHO's strategic plan for enhancing global vaccine safety activities. The study targeted 11 national vaccine safety systems (NVSSs)[1] as well as 13 international vaccine safety initiatives (IVSIs)[1] for the year 2009. However, due to data availability, data analysis is only provided for five countries out of the eleven (Brazil, the Islamic Republic of Iran, Mexico, Senegal and Uganda).

National vaccine safety systems costs and funding (Brazil, Iran, Mexico, Senegal and Uganda)

Results showed that the average cost of vaccine safety system per vaccine doses administered was US$ 0.03 on average per country (from US$ 0.0014 in Uganda to US$ 0.0648 in Mexico).

The cost per fully immunized child was US$ 0.53 on average per country (from US$ 0.01 in Uganda to US$ 1.37 in Iran). Countries identified as having well-established AEFI surveillance systems (Brazil, Iran and Mexico) had the highest total costs in comparison to other systems (Senegal and Uganda). Middle-income economies had a relatively higher cost of their NVSSs. Personnel were by far the largest contributor, at 81% of the NVSS total costs (from 50% in Uganda to 97% in Iran). Shared personnel were the main cost driver, accounting for 68% of total costs on average (from 38% in Brazil to 94% in Iran). Specific personnel represented 13% of total costs on average per country (from 0% in Uganda and Senegal to 54% in Brazil).

[1] Albania, Brazil, India [Maharashtra state], the Islamic Republic of Iran, Kazakhstan, Mexico, Senegal, Sri Lanka, Tunisia, Uganda, and Viet Nam.

[2] WHO Global Network for Post-Surveillance of Newly Prequalified Vaccines; national regulatory authority assessment (WHO); CIOMS/WHO working group on vaccine pharmacovigilance; case definitions and guidelines for adverse events, Brighton Collaboration (BC); automatic case verification (BC); Global Vaccine Safety Data Link (GVSD); background rate of concern verification (BC); Global Vaccine Safety Data Link (GVSD) – hypothesis testing studies (BC); vaccine safety crisis management / rapid response team (WHO),;vaccine safety training (WHO); WHO Global Advisory Committee on Vaccine Safety (GACVS); project to support public confidence in immunization programmes(LSHTM).

The most important system component in terms of costs was investigation, which accounted for 35% of total costs on average per country (from 14% in Senegal to 68% in Mexico). The second largest system component contributor to costs was detection, which contributed 27% of costs (from 2% in Uganda to 66% in Brazil). Coordination also accounted for 27% of costs on average (from 6% in Mexico to 67% in Senegal).

Regarding the funding of NVSSs, Senegal and Uganda relied mostly on external donor support. By contrast, NVSSs of Brazil, Iran and Mexico had a low donor dependency as they were mainly funded by the MOH.

International vaccine safety initiatives costs and funding

The total cost for all IVSIs was US$ 4.3 million. IVSI focused mainly on coordination which accounted for the majority of the costs (55%; US$ 2.38 million). Investigation was the second most important system component (23%; US$ 1 million). Personnel costs (i.e. salaries and per diems) were the main specific cost category of IVSIs at 64% of the total costs. Training was the second most important (16%) followed by transportation (13%) and equipment (4%).

The Bill & Melinda Gates Foundation contributed the largest amount for IVSIs, at US$ 1.2 million, and was the most frequent IVSI funder, providing support to six initiatives out of the 13. The NRA assessment initiative had the most diverse funding sources (12 funders). All other IVSIs relied on between one and four funding sources to conduct their activities. The major IVSI funders mostly supported coordination, whereas detection, investigation and communication represented a minor share of their financial support.

1. Introduction

The goal of the study was to provide data on the cost and funding for current vaccine safety systems in low- and middle-income countries (LMICs), and international vaccine safety initiatives. These data were collected to inform decisions on budgets and funding choices for WHO's strategic plan for enhancing global vaccine safety activities.

The financial assessment sought to provide answers to the following questions.

- How much does the current vaccine safety system cost? What are the main cost drivers?
- Which of these costs are likely to reoccur each year or to increase following improvements in vaccine safety systems?
- How much is spent by vaccine safety initiatives and vaccine safety technical and financial partners worldwide? In which specific areas of vaccine safety do each of them invest?
- How is the coordination between financing partners perceived by vaccine safety stakeholders?
- To what degree do stakeholders perceive funding mechanisms as operational and efficient?
- What other funding mechanisms could be proposed?

2. Methodology

2.1 Scope of the study

The period for which costs were considered was the year 2009. The spatial scope included 11 NVSSs and 13 IVSIs, worldwide. The perspective of the financial assessment was that of ministries of health of selected countries and IVSIs (i.e. the main organizations conducting vaccine safety activities at the global level).

2.2 Cost calculation methodology and analysis

For cost calculation, three different methodologies were adopted; the ingredient approach, the rule-of thumb and the budgeting approach. The ingredient approach was chosen based on the assumption that the two cost categories, personnel and transportation (shared and specific), were likely to represent the bulk of resources used for activities; as such, it needed to be assessed in the most accurate way possible. This approach was further justified by the fact that most resources are shared with other programmes and that no budget line is available. The rule-of-thumb approach was used for overheads or small materials as they were likely to represent a minor share of the cost. The budgeting approach was applied for training and equipment of IVSI. The exchange rate used was the 2009 annual average rate for the local currency versus US dollar currency. No inflation rate was taken into consideration due to the fact that the study was conducted during a one-year period.

Costs were calculated by NVSS (and for all NVSS) and by IVSI (and for all IVSI). The following costs were provided by the financial assessment:

- total costs (by system components, activities, cost categories);
- average costs per vaccine doses administered, per fully immunized child, per AEFI reported (by system components, activities, cost categories);
- shared versus specific costs — to identify which costs are shared with other programmes;
- fixed versus variable costs — to identify which costs are likely to increase following improvements in vaccine safety systems;
- recurrent versus capital costs — to identify which costs are likely to reoccur each year.

2.3 Methodology for the analysis of funding strategies

The funding for vaccine safety was analysed by system component and activities based on the opinions of both national and international vaccine safety experts. The following criteria were used for the assessment.

- Efficiency: a situation where the costs of obtaining and accounting for funds and stimulating efficient vaccine safety activities are minimized.
- Capacity to provide resources in a timely manner and in the right place: a situation where resources are available in the desired volume at the right time and at the right place to have the greatest benefit for vaccine safety.
- Overlap: a situation where the same activities are funded by different initiatives leading to a surplus in funding for those activities (in relation to needs).

- Sustainability: the ability to mobilize and use resources in an efficient and reliable manner to achieve current and future vaccine safety targets.
- Accountability: a financing arrangement that is compatible with procedures, and documentation that allows for transparency in the allocation and use of funds.

2.4 Data collection

The survey participants for data collection (individuals and institutions) were vaccine safety experts identified by the collaborative group. For the countries, the survey respondents were the national focal points for the Global Network for Post-Marketing Surveillance. For international initiatives, they were the heads of the different IVSIs. The questionnaires were sent by email to survey participants, in addition to guidelines on the completion of the questionnaire. The preliminary costs calculated were shared with the countries' focal points and IVSIs for their review and validation, and then revised accordingly.

2.5 Study limits

The survey is limited to five countries, as in six of the surveyed countries (Albania, India, Kazakhstan, Tunisia, Sri Lanka and Viet Nam) it was not possible to determine the total costs for vaccine safety activities. Consequently, due to the limited sample size, the total and average transversal costs calculated for NVSSs are only indicative. In addition, some of the results of the study (e.g. cost per AEFI reported) are dependent on AEFI reporting. As a result, average cost per AEFI can be either under or overestimated.

The contributions and activities of vaccine producers were not in the scope of the financial assessment as the perspective chosen was the one from the Ministry Of Health. This perspective might have underestimated resources for AEFI surveillance, as some are provided by manufacturers (for activities of post-marketing surveillance, characterization and understanding of serious adverse events related to vaccines).

3. Costs and funding of national vaccine safety systems

3.1 National vaccine safety systems total and average costs

Countries identified as having well-established AEFI surveillance systems (Brazil, the Islamic Republic of Iran and Mexico)[3] had the highest total costs[4] in comparison to other countries' systems (Senegal and Uganda). The NVSS total cost was US$ 0.9 million in 2009 on average per country (from US$ 10 012 in Senegal to US$ 2.4 million in Iran). In 2009, the cost per vaccine doses administered was US$ 0.03 on average per country (from US$ 0.0014 in Uganda to US$ 0.0648 in Mexico). The cost per fully-immunized child was US$ 0.53 on average per country (from US$ 0.01 in Uganda to US$ 1.37 in Iran). Table 1 shows that, without shared personnel, the average cost per fully-immunized child falls to US$ 0.09 on average per country.

[3] See activity 1.5 baseline assessment (structure and management of AEFI system.

[4] Three different methodologies were adopted for cost calculation: the ingredient approach (for personnel and transportation); the rule-of-thumb approach (for overheads and small material costs), and the budgeting approach (for training). Vaccine safety activities were divided into four system components (type of activities): detection; investigation; communication, and coordination.

Among the countries surveyed, low and lower-middle income countries had lower cost of their NVSSs. However, a low cost per vaccine administered or fully-immunized child, may indicate either an efficient system or an underfunded system, or one that does not conduct the required activities. Given that, by far the lowest costs per fully-immunized child, occurred in the countries with the least resources, the latter explanation seems more likely. The low cost of these NVSSs could imply a need for surveillance capacity strengthening (especially in terms of detection and notification activities at the health-care delivery level to ensure a proper reporting system). This was the case with Senegal and Uganda, where the detection system component accounted for a lower share of total cost. Another finding that could suggest underfunded systems is, that there seemed to be a common trend between the importance of the cost for detection and the number of AEFIs reported.

Table 1: National vaccine safety systems average cost per system component in 2009 (US dollars)

SYSTEM COMPONENT	COST PER VACCINE DOSE ADMINISTERED (US$)		COST PER FULLY-IMMUNIZED CHILD (US$)		COST PER AEFI (US$)	
	With shared personnel	Without shared personnel	With shared personnel	Without shared personnel	With shared personnel	Without shared personnel
DETECTION	0.0071	0.0009	0.1677	0.0343	299.32	109.36
INVESTIGATION	0.0133	0.0011	0.2288	0.0265	1362.18	244.74
COMMUNICATION	0.0034	0.0001	0.0609	0.0008	163.38	6.97
COORDINATION	0.0032	0.0007	0.0581	0.0141	283.27	91.60
OTHER	0.0009	0.0007	0.0164	0.0138	113.67	53.61
TOTAL	0.0278	0.0034	0.5320	0.0893	2221.83	506.28

3.2 National vaccine safety systems system components costs

The most important system component in terms of costs was investigation, which accounted for 35% of total costs on average per country (from 14% in Senegal to 68% in Mexico). The second largest system component contributor to costs was detection, which contributed 27% of costs (from 2% in Uganda to 66% in Brazil). Coordination also accounted for 27% of costs on average (from 6% in Mexico to 67% in Senegal).

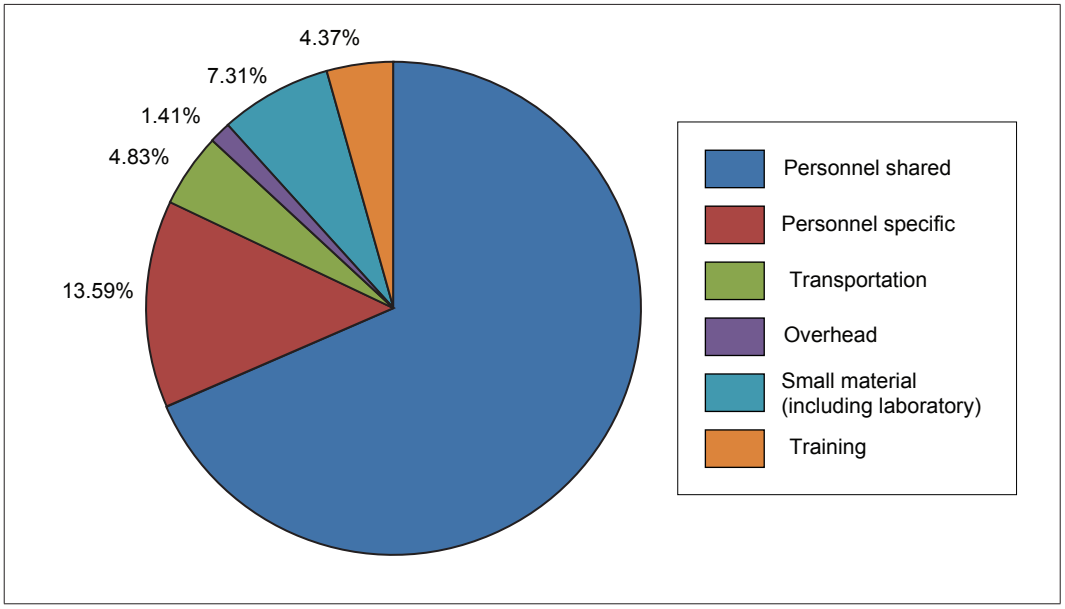
A common factor identified between all the countries is the low cost of communication in relation to other system components, as communication represented, on average, 5% of total costs (from 0% in Brazil to 15% in Iran).

3.3 *National vaccine safety systems costs driver (by cost category)*

The main costs driver of NVSS is personnel. It represented 81% of the total costs on average (from 50% in Uganda to 97% in Iran). Most of these personnel were shared personnel working on some other activities — it represented 68% of total costs on average (Graph 1) ranging from 38% in Brazil to 94% in the Islamic Republic of Iran. Specific personnel represented 13% of total costs on average per country (from 0% in Uganda and Senegal to 54% in Brazil), reflecting the existence in some countries of positions dedicated to AEFI surveillance activities.

Most of the costs of the NVSS did not change with a variation in the degree of vaccine safety activities because they were fixed costs (68%). In addition, costs were mostly shared (68%) with other programmes, which meant that they were not directly paid for (but were funded by other programmes)[5].

Graph 1: Distribution of national vaccine safety systems costs, by cost category in 2009 (percentage)



3.4 *National vaccine safety systems funding*

Regarding the funding of NVSSs, the donor dependency was different between countries. Senegal and Uganda mostly relied on external donor support, but, by contrast, NVSSs in Brazil, the Republic of Iran and Mexico, had a low donor dependency as they were mainly supported by the MOH. National health ministry's[6], in particular, supported investigation for 23% of total NVSS funding and detection for 26% on average per country. WHO supported coordination at 21% on average per country, and this was even higher in Senegal and Uganda.

[5] The absence of capital costs is linked to the assumption that no equipment costs are purchased specifically for NVSSs.

[6] The specific activities from manufacturers in terms of AEFI surveillance were not included in the scope of the survey.

3.5 To go further on national vaccine safety systems results

- In absolute terms, and all things being equal, if the vaccine price were raised by US$ 0.03 per dose, the cost of current vaccine safety activities at national level would be covered, as it represents the average cost per dose of all the NVSS activities conducted (on average per country).
- Funding requirements for functional NVSSs could be determined by the average cost provided by the financial assessment representative of existing AEFI surveillance systems and, in particular, the average cost per fully-immunized child, in relation to vaccine coverage targets in countries (all things being equal).

It may be preferable to use the average costs of countries with the most effective vaccine safety activities. In this case, data from Brazil, as well as the Islamic Republic of Iran and Mexico, might be more appropriate.[7]

4. Costs and funding of international vaccine safety initiatives

4.1 IVSI total cost and system component costs

At the global level, the total cost for IVSIs was US$ 4.3 million. Coordination accounted for the majority of the costs (55%; US$ 2.38 million). This, in turn, was mainly driven by development of guides and tools (17% of total), committees and meetings (11%) and capacity building (6.5%). Investigation was the second most important system component (23%; US$ 1 million) and was mostly driven by hypothesis-testing studies (14%). Communication accounted for US$ 0.05 million (1%). The distribution of the IVSI system components can be explained by the fact that international initiative core activities are related to support national AEFI surveillance[8]. As a matter of fact, the low cost share of detection is due to the fact that consultation and notification are conducted at national level, where they account, on average, for 27% of activity costs.

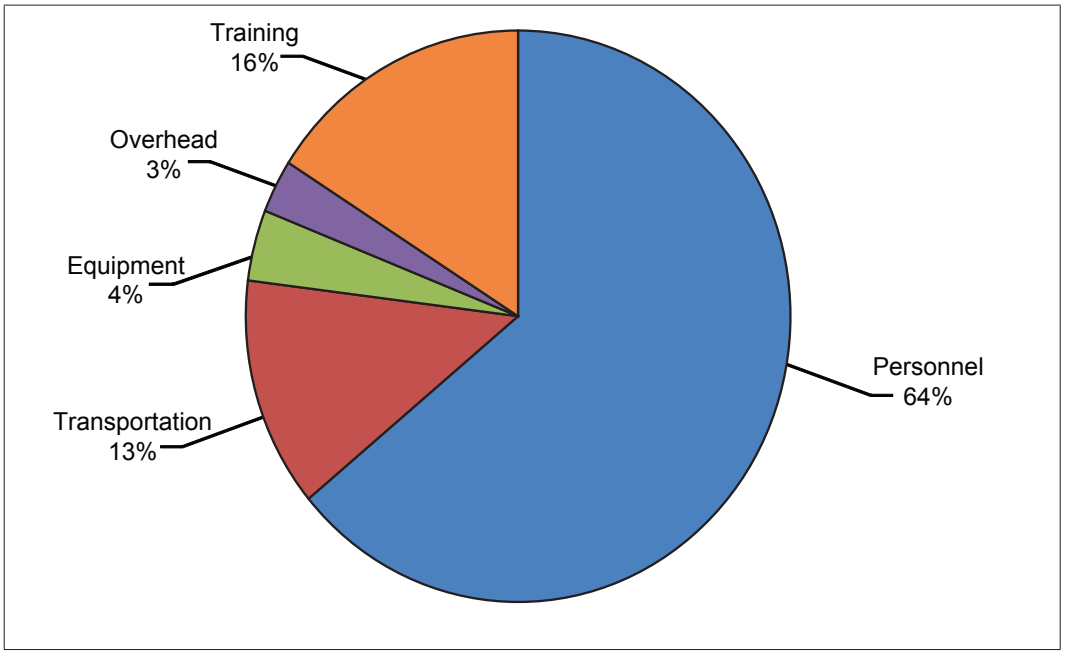
4.2 International vaccine safety initiatives costs drivers (by cost category)

Personnel costs (i.e. salaries and per diems) were the main cost category of IVSI at 64% of the total costs. Training (including capacity-building activities) comes second (16%), followed by transportation (13%) and equipment (4%).

[7] As they were identified as having well-established systems by activity 1.5.

[8] According to the results of the SWOT analysis 1.2, IVSI "*provide services to the national level towards specific goals [...] concern detection to concern validation to hypothesis testing to risk communication*."

Graph 2: Distribution of IVSI costs by cost category in 2009 (percentage)



4.3 International vaccine safety initiatives funding

The institutions supporting IVSIs financially included: foundations; UN organizations; global-health partnerships; national governmental institutions; specialized agencies; bilateral agencies; multilateral agencies, and private donors, with a total of 17 different funders. Seventy-seven percent of the IVSI funding is provided by four of these organizations. The NRA assessment initiative had the most diverse funding sources, with 12 different funders. All other IVSIs relied on between one and four funding sources to conduct their activities.

The Bill & Melinda Gates Foundation was the most frequent IVSI funder, providing support to six initiatives and supporting the four types of system components. Almost all major funders supported coordination, with the exception of the European Centre for Disease Prevention and Control, which primarily supports investigation. The Bill & Melinda Gates Foundation, WHO and the GAVI Alliance, contribute 10% to 20% for investigation and 80% to 90% for coordination.

4.4 To go further on international vaccine safety initiatives results

While IVSIs contributed over US$ 4 million, the findings from individual countries indicate how limited this amount is, as it approximates the amount spent by just the Islamic Republic of Iran and Mexico. The overall amount spent by the different organizations that fund IVSI is also tiny compared to that spent promoting vaccines. For example, the Bill & Melinda Gates Foundation contributed the largest amount at US$ 1.2 million, for which they are to be commended; however, within the context of a multi-billion initiative to develop or introduce new vaccines, this amount is small. Even more striking is the amount contributed by the GAVI Alliance, at just over US$ 400 000, and the United States Agency for International Development (USAID) and arms of other sovereign governments, in which major vaccine manufacturers reside.

One consequence of the small total amount contributed to vaccine safety is that IVSIs focused mainly on catalysing vaccine safety systems rather than directly supporting or financing national systems. For example, just US$ 104 000 was spent on case investigations. By contrast, activities such as capacity building, committees and meetings, and development of guides and tools received substantially greater funding.

5. Financing strategies for vaccine safety

5.1 Evaluation of the current funding systems of vaccine safety activities

The assessment of the current vaccine safety funding situation by experts[9] is that:

- adequacy of funding: vaccine safety is not sufficiently funded.
- Timeliness of funding: funding for vaccine safety activities was not available at the right time or at the right place (for 60% of the respondents). Diminishing budgets, insufficient resources and delays for material and budget delivery were reported by survey respondents as obstacles to funding timeliness.
- Overlap: there is no overlap in current financing for vaccine safety (for 66% of countries' experts and 60% for experts from initiatives).

International experts indicated that increased political will and the sustainability of funds are the most important criteria related to success, and hence that these should assume priority in developing a financing strategy for vaccine safety.

This suggests that all types of activities are either in need of financing[10] and/or that they can absorb additional funding. The other implication is that a financing strategy that would reallocate funds from activities already conducted, to others, is not an option for the future financing strategy.

The combination of low current funding in developing countries, low funding by international donors, and an imperative for countries to implement robust surveillance in the future, creates a conundrum. The NVSS and IVSI experts have provided some recommendations for moving forward, which focus mainly on strategies for increasing funding. Ideally, in the long term, all countries would contribute a sufficient amount for national activities.

[9] Among the 19 experts contacted to provide their comments on the current financing situation of NVSSs and IVSIs, 15 provided answers and recommendations (8/11 from NVSS and 7/8 from IVSI). These experts included national vaccine safety experts (national EPI managers, national AEFI surveillance managers, etc.) and heads of international vaccine safety initiatives.

[10] The need for financing is confirmed by the financial results of activity 1.2 (SWOT+ analysis) that indicated an expansion in the planned FTE of 30%.

5.2 Recommendations for the funding strategy

Recommendations from vaccine safety experts were all oriented towards increasing funding. The main ones were:

- to create a dedicated budget for AEFI surveillance;
- to implement a combination of public and private funds;
- to explore the feasibility of an excise tax model;
- to explore the feasibility of a predefined regular contribution managed by WHO or an international regulatory authority.

6. Conclusions

Countries identified as having well-established AEFI surveillance systems (Brazil, Iran and Mexico) had the highest total costs in comparison to other systems (Senegal and Uganda). In addition, middle-income economies had a relatively higher cost of their NVSSs. The main cost category of NVSS was shared personnel (68%). The average cost per vaccine doses administered was US$ 0.03 on average per country (from US$ 0.0014 in Uganda to US$ 0.0648 in Mexico). The cost per fully-immunized child was US$ 0.53 on average per country (from US$ 0.01 in Uganda to US$ 1.37 in Iran). At the global level, the total cost for IVSIs was US$ 4.3 million. Coordination accounted for the majority of the costs at US$ 2.38 million (55%). Investigation was the second most important system component with a cost of US$ 1 million (23%).

The results of this study can provide guidance for estimating funding requirements for future vaccine safety activities. It must be balanced by the assessment that some of the reporting countries were likely to have underfunded systems. Outcome indicators for vaccine safety systems are lacking, and make it difficult to judge which systems are functioning well with adequate funding.

For NVSSs, these results indicate the overall contribution and main cost drivers within different country contexts, which may help guide financing strategies in the future. For example, the main cost category in most countries was human resources. By contrast, Mexico, and to a lesser extent the Islamic Republic of Iran, contribute substantial resources to communication. Given that a major reason to conduct AEFI surveillance is to reassure the public, efforts might be made to encourage countries to spend more on communicating results of surveillance to providers and the public. The overall costs of AEFI surveillance in more developed economies, such as Brazil and Mexico, may also provide guidance on the costs of more robust systems. In order to interpret performance of NVSS, it would be interesting in future studies to show the distribution of the activities' costs at the different administrative levels.

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

Department of Immunization, Vaccines and Biologicals

Family and Community Health

World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland
E-mail: vaccines@who.int
Web site: http://www.who.int/immunization/en/